Metascience in Dentistry and Medicine

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Abbreviations

ADA	American Dental Association
AHI	Apnea-hypopnea index
AHRQ	Agency for Health Research Quality
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
EBD	Evidence-based dentistry
ICSD-3	International Classification of Sleep Disorders, Third Revision
MAOA	Mandibular advancement oral appliances
OSA	Obstructive sleep apnea
SARS-Cov-2	Severe acute respiratory syndrome coronavirus #2
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint

1.1 Introduction

Almost half a century ago, in 1972 to be exact, British physician and epidemiologist Archibald Cochrane published *Effectiveness and Efficiency: Random Reflections on Health Services*, in which he made a provoking and seminal observation: "It is surely a great criticism of our profession that we have not organized a critical summary by specialty or subspecialty, adapted periodically, of all relevant randomized

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clinical trials." That statement summoned the medical community internationally to the general call of systematically organizing the wealth of medical research available to clinicians to aid their decision-making in practice.

Twenty years later, the term "evidence-based medicine" was introduced by Guyatt and collaborators with an emphasis to shift clinical decision practice in medicine from what they described as "intuition, unsystematic clinical experience, and pathophysiologic rationale" to science-based, clinically relevant facts. By the end of the millennium, in 1999, the American Dental Association proffered a definition of the term "evidence-based dentistry" as the approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences [1].

Concerted research during the past two decades have defined and characterized the protocols of comparative effectiveness research—from the research synthesis design to the systematic generation of the bibliome and its assessment of research quality and acceptability quality to the production of the qualitative and quantitative consensus of the best evidence base—which have been well described [2, 3] and used in the context of temporomandibular joint disorders and obstructive sleep apnea [4].

1.2 Metascience

The roots of Western science are to be found in the philosophers of ancient Greece and Rome. Their observations of matter, energy, and diverse phenomena on earth and in the heavens, and the interaction between them, constituted what they referred to as the study of nature or physics. Soon, they expanded their inquisitive horizon to the identification of what lied behind or above the physical forces of nature; that is, what was "meta"physical. Metaphysics helped characterize the fundamental nature of reality, the relationship between mind and matter, and the distinction between substance and attribute. Metaphysics enabled thinkers to distinguish potentiality from actuality, reality from perception, and science-based phenomena from biased beliefs.

The prefix "meta" informs the study of the principles that drive a given domain of inquiry as much in metaphysics as in cognitive psychology and other fields. Case in point, the study of cognition pertains to elucidating the nature of knowing, and the mental processes that contribute to knowing, from awareness and perception to reasoning, inductive and deductive inference, and intuitive judgment. But metacognition pertains to the systematic examination of the processes of cognition: it is gaining knowledge about cognition, that is, cognition about cognition itself and thinking about thinking. Metacognition pertains to the study of the metal processes, from awareness to judgment, of the very higher intellectual skills and events that constitute cognition.

Metascience was similarly defined as the systematic uncovering, building, organizing, and disseminating of science-based knowledge that was obtained, tested,

and verified through the scientific process in the first place. Metascience is the very scientific inquiry into science itself [3]. Metascience informs a universal system to organize Cochrane's critical summary by specialty or subspecialty, adapted periodically, of all relevant best research evidence, to integrate it with patients' values, needs, and wants, and clinical circumstances and with the clinician's clinical expertise to generate a treatment plan that is science-based, focused on optimizing effectiveness, and centered on the specific clinical needs of the patient.

Metascience is grounded on research to yield the best evidence base to benefit patient care, minimize misdiagnosis, and ensure the best decision-making regarding procedures and treatments. It is structured in its protocol, but flexible in the dissemination of its findings, and therefore when best adapted actively involves the stakeholders by all possible means, including telemedicine and tele-dentistry modalities [3].

1.3 Defining the Bibliome

The evidence-based process in medicine and dentistry and healthcare in general for that matter proceeds in a series of well-defined steps, which begin by obtaining the entire universe of published and unpublished evidence that pertain to a given clinical case. A systematic process of inclusion and exclusion, adding and refining of the evidence, yields a body of work that addresses the case along specific dimensions that define and determine the nature of the research question, as outlined below. The specific body of work that addresses the clinical dimensions determined by the question is called the bibliome [2].

To be clear, healthcare research is constantly evolving and expanding. Therefore, the bibliome for any given clinical case has the potential of being in constant flux. It follows that evidence-based research is always defined and determined in a given span of time: that is to say, a research synthesis report must state the time frame within which it purportedly proffers the best available evidence.

1.3.1 Stating the Question

The process of evidence-based medicine/dentistry commences by, and in grounded in, asking the right research question, which opens the systematic research synthesis design. As noted, the process is patient-centered. Therefore, the first domain that is addressed by the research question pertains to the patient under treatment and the patient group or subgroup and population or subpopulation that patient represents (e.g., men, woman, child, elderly, ethnicity, with preexisting diabetes, with history of cancer, and the like). To be clear, that description of the patient, P, also includes a detailed description of the clinical problem for which the best available evidence is sought.

Secondly, the research question entertains possible interventions, I, which the clinical is considering (e.g., remdesivir for the patient positive for SARS-Cov2 or

monoclonal interleukin-10 administration to muffle the cytokine storm in the same patient and the like).

Metascience is a science-based experimental approach [3]. It follows that it must entertain a control, C. The control group in the research synthesis design consists of the evidence on treating the clinical problem, P, with alternate interventions. For example, in the case proposed above, C might involve comparing the evidence on remdesivir with the evidence on Theraflu, as a control antiviral, for the SARS-Cov2-positive patient or comparing the evidence on monoclonal interleukin-10 administration to muffle the cytokine storm with the evidence on using Tylenol to contain and suppress inflammatory cytokines.

A question is always driven by what outcome, O, it pursues. In the context of research synthesis, the outcome sought is the best available evidence in support of the clinical aims desired in the first place (e.g., improvement of the COVID-19 patient clinical status or containment of the cytokine storm).

Often, although not always, clinical directives demand that the outcome be obtained within a certain timeline, T, and a given clinical setting, S (e.g., private office vs. hospital setting).

Taken together, these elements of the research question in evidence-based medicine/dentistry are subsumed in the acronym P-I-C-O(-T-S). It is based on the detailed elements contained in P-I-C-O(-T-S) that the research evidence is searched and subjected to rigid criteria that define inclusion and exclusion boundaries [2].

1.3.2 The Analytic Framework

The resulting P-I-C-O(-T-S) statement is formulated as the research question of the systematic review of the evidence. As customary, the research question is also a statement of the study hypothesis, by definition. That is to say, metascience, research synthesis, and the process of systematic review that engenders the evidence-based medicine/dentistry is hypothesis-driven because it is P-I-C-O(-T-S)-driven [2, 5–11].

The P-I-C-O(-T-S) question is validated and expanded by means of an analytical framework uniquely designed to interrogate in depth each specific domain that constitute the P-I-C-O(-T-S) statement under consideration. Certain keywords and phrases that aid in pinpointing the exact scientific evidence that pertains to the research question are generated in this manner, which inform the refinement of the bibliome.

The pertinence of each uncovered report to the research question is verified by two independent assessors: reports that are pertinent to the intent of the P-I-C-O(-T-S) question are retained; those that are not are excluded from the bibliome. Generally, the bibliome is restricted to peer-reviewed publications; but for the sake of completeness, additional information obtained by direct contact with the authors, prereviewed publications, or even "gray" literature may be included as qualifiers to conclusions presented in the final discussion of the findings of the systematic review.

In brief, the preliminary bibliome that results from a wide multi-database search based on the criteria stated in P-I-C-O(-T-S) is refined by stringent inclusion/

exclusion criteria derived from the analytic framework, thus yielding the bibliome that is directly and uniquely pertinent to the research question. The bibliome is then subjected to a systematically stringent evaluation of the level and the quality of the evidence.

1.4 Capturing the Best Available Evidence

Tools have been developed, refined, and validated to establish the level of the evidence, that is, to identify those studies in the bibliome that are endowed with the highest level of evidence, clinical trials have the highest level of evidence, followed by cohort observational studies, and the strongest quality of the evidence in terms of adherence to the principles of sound research. The best evidence, once identified, is subject to critical appraisal, quantification, and statistical analysis for acceptability and for overall significance, including the principles of data extraction, and models meta-analytical inference (e.g., fixed vs. random models). Protocols follow to translate statistical significance of the best available evidence into clinical relevance following a qualitative and quantitative consensus process that validated and summarized in the critical summaries available to the clinicians, transliterated into lay language, and disseminated to the patients and caregivers.

Capturing the best available evidence must inform evidence-based treatment plan design and administration. Evaluation of the outcome of the evidence-based intervention is the ultimate test of effective capture of the best available evidence.

1.4.1 The Level of the Evidence

The level of the evidence refers to the type of study, clinical trial, experimental, observational, correlative, or longitudinal. The principal instrument was first proposed by Moher and collaborator (2001) and named the Consolidated Standards of Clinical Trials. It was revised and updated in 2010 [12, 13] and validated as a shortened and faster version [14].

CONSORT-10 was also incorporated in a similar instrument designed to quantify the level and the quality of systematic reviews and meta-analyses [15, 16]. An evolution of CONSORT and PRISMA has led to the validation of the Cochrane's risk of bias assessment.

1.4.2 The Quality of the Evidence

The quality of the evidence refers to the nature of the data obtained, the structure of the sample that generated the data, the validity and reliability of the measuring instruments that produced the data, and the exactness of the statistical analysis of the data. Quality of the evidence can be quantified by a variety of instruments, we and others have endeavored to validate over the years [2, 6, 8], from the Assessment

of Multiple SysTemAtic Reviews (AMSTAR) and its revised formulation [17] to the GRADE instrument and its revision [18] and to the assessment of the risk of bias and its evolution [19].

1.5 Analysis

One essential aspect of evidence-based research is that the instruments used in the estimation of the level and quality of the evidence be at least semi-continuous (e.g., in the form of the Likert scale, with responses ranked 1–4). "Yes/no" answers can be transformed to a 1 or 2 scale. But qualitative responses cannot be used in an analytic dimension, unless they are subjected to a cluster transformation of the type we have proposed, which is admittedly weak and generally less than satisfactory [20].

1.5.1 Acceptable Sampling

One of great utilities of statistical analysis is its ability to dive within the information to elucidate the truth principally by minimizing that which is erroneous**.** The "best" reports are obtained by means of a stringent acceptable sampling statistical analysis, commonly referred to as meta-analysis. The validity of these analyses is repeatedly evaluated by means of formative and summative evaluation, and updated as required, because it is self-evident that scientific research in every field is an active and ongoing process [8].

1.5.2 Overarching Statistical Significance

Meta-analysis is the statistical analysis that combines the results of multiple scientific studies. It is a complex subfield of statistics in its own right, with stringent assumptions, computation, and interpretative models, limitations, and validity threats [21]. Nonetheless, when judiciously utilized, it is a strong tool to uncover common threads of statistical significance among homogeneous studies, which then translate into powerful statements about the statistically significant best available evidence [2, 7, 8, 22].

1.5.3 Clinical Relevance

Evidence-based practice rests largely on clinical relevance. To be clear, statistical significance informs the best available evidence that ought to be considered in clinical decision-making. But if statistically significant evidence fails the criterion of clinical relevance, it is often of little value in the evidence-based treatment plan. As noted above, statements of clinical relevance can be quantified and cluster-analyzed

[20], but that is an artificial process, a spurious manipulation of data and findings likely to generate bias and fallacies.

In brief, clinical relevance is best assessed by the clinicians but that requires that they be sufficiently familiar with research synthesis and metascience captures the essential nature of the best available evidence. Clinical relevance should be derived only from the reports that have been vetted through the process of the level and the quality of the research and that have emerged as the consensus of best available evidence.

There are several approaches to obtain consensus on the best available evidence.

- The RAND Corporation proposed four distinct stages to reach a qualitative consensus:
  - Stage 1: Develop an initial set of indications for undertaking a procedure based on the literature review and discussions with experts in the field to include ultimately all the indications for a given procedure that might arise in practice.
  - Stage 2: The list of indications is circulated independently to a panel of expert reviewers, who are provided with a literature review to rate the appropriateness of indications for a given procedure and to consider implications and utilization in specific clinical settings of a typical general practice within the United States (i.e., translational effectiveness).
  - Stage 3: Panelists reach a modified Delphi consensus approach, whereby ratings range from 1 (extremely inappropriate) to 9 (extremely appropriate), where appropriateness is defined as the expected health benefit to the patient (relief of symptoms, improved functional capacity, reduction of anxiety, etc.). Expectations are that this protocol can reduce the range of responses and arrive at something closer to expert consensus. This is followed by a face-to-face meeting, and the results of the ratings are passed around and unlabeled, so only the individuals know their own rankings. After group discussions and revisions of the indications, the panels rate the indications again and as previously are brought together for a face-to-face meeting, and the results of the ratings are passed around so that panelists may reconsider their judgment in light of clinical evidence and translational effectiveness.
  - Stage 4: The degree of consensus of the panel can be estimated by calculating the average dispersion measures for the procedures.
- The now disbanded National Institutes of Health Consensus Development Program formerly proposed a method by which the scientific community could bring relevant research to bear on the quality of healthcare in a process that was aimed to bring clinical practice more in line with research and eventually to get consensus statements on the best evidence base by a panel of expert reviewers.
- Qualitative consensus may also be obtained by text mining analysis—that is, the science of obtaining and quantifying information from text (i.e., information retrieval, lexical analysis to study word frequency distributions, pattern recognition, tagging/annotation, information extraction, data mining techniques

including link and association analysis, visualization, and predictive analytics). The goal is to quantify for use in predictive or quasi-predictive analyses. Content analysis (www. Content-analysis.de) is a software that supports text interpretation as well as text management and the extraction of conceptual knowledge from documents (theory building), with large bodies of textual and graphical data, such as that of systematic reviews. MAXQDA 1 (www.Maxqda.com) is a powerful software especially suitable for projects working with mixed-methods approaches, for example, such as those that arise from complex systematic reviews or complex sets of data with multiple groups and subgroups.

The product of research synthesis must be, in terms of its application in clinical practice, not only cumulative but more importantly patient-centered and focused on cost and benefit effectiveness. It follows that the Markovian, utility-based, and probability-grounded clinical decision-making may not always be optimal. Rather, the logic model of clinical decisions seems better apt in integrating evidence-based recommendations as we have defended elsewhere. The logic process of decision for evidence-based dentistry treatment may involve several stakeholders, who may serve a variety of important functions including helping to formulate key questions that address real-world dilemmas in terms of efficiency of treatment, cost, and benefit effectiveness, functionality and appearance of restoration, and the like, and provide a more appropriate context to help discern content areas and applicability [2, 8, 23].

It follows that one critical aspect of clinical relevance is the importance of the role played by the stakeholders in evidence-based practice. Stakeholder engagement is difficult but not impossible to measure [24, 25] because of the complexity of all facets of the translation of evidence-based dentistry research outcomes and integration in evidence-based dentistry practice. The role of stakeholders in evidence-based dentistry practice is even more significant when one considers the relevance of the evidence-based paradigm in translational healthcare. A recent systematic review has confirmed the important contribution of discrete choice experiments as a tool for engaging stakeholders in implementing the best available evidence in evidence-based medicine and evidence-based dentistry [25].

Specifically, the process of translational science [8] in healthcare can be defined and characterized as a four-tier process simply rendered as follows:

- Tier one (T1), also referred to as translational phase 1, initiates TB1, the process from the patient-clinician encounter to the bench, patient, and community of stakeholders. T1 usually involves preclinical studies from participant observations and case-control studies to in vitro and animal experiments and to observational cross-sectional and retrospective or prospective cohort studies to eventually phase 0, 1, and 2 clinical trials.
- T2 expands the discovery phase by means of study designs with larger patient populations, such as cohort observational, phase 3 and 4 clinical trials and observational studies.

- T3 launches TB2, the translational effectiveness-oriented stage of the process, which seeks to establish whether certain treatments or practices work in specific clinical settings.
- T4 focuses on identifying and characterizing the optimal existing standard operating procedures, that is, the best practices for reaching clinicians, patients, and all stakeholders with a nationwide policy concerning treatment X or strategy Y: that is to say, translating the best evidence base on treatment X or strategy Y into widely disseminated evidence-based revisions of clinical practice guidelines and policies, while optimizing stakeholder health literacy and engagement. To be clear, translational research and translational effectiveness represent two distinct facets of one and the same construct of translational science [2, 8].

1.6 Reporting and Dissemination

Metascience is reported and disseminated by several means and at several levels**.** Formal systematic reviews are peer-reviewed and published in specialized academic journals. These are typically long and complex technical reports of the research synthesis process, statistical analysis of the findings, and discussion of clinical relevance. They are rich in methodology details that permit replication, complex and detailed analyses and interpretations, and arguments about research efficacy, clinical effectiveness, and overall efficiency.

1.6.1 Dissemination for Clinicians and Researchers

Critical summaries of systematic reviews are shorter documents that typically do not exceed two to three printed pages. They are written for the clinicians primarily and summarize the metascientific research protocol and its findings. These documents generally outline the implications for clinical effectiveness and expand on the clinical relevance of the findings. They are written by and for experts in the field in metascientific jargon, published in peer-reviewed journals, and have the prime purpose to aid the clinician to optimize evidence-based patient-centered recommendations.

One special domain of dissemination of the best available evidence, which has found most fertile grounds in the aftermath of the COVID-19 pandemic, is telehealthcare. The fast-developing technology of telehealth, and specifically in the context of evidence-based medicine/dentistry, and teleconsultation for evidence-based healthcare consists of a low-cost and low-bandwidth exchange of information between health specialists and patients and caregivers and stakeholders when specialists are not available and is among the most common type of health service in both developed and developing countries [2, 8]. Expectations are that in the next 20 years, it will develop into a fundamental tool that will benefit patients by providing improved seamless interconnectedness among clinical professionals and direct

hack-free access to patients in critical needs. In short, tele-evidence-based healthcare will greatly increase treatment care effectiveness for patients across national, social, ethnic, and economic boundaries, while ensuring individualized patient-centered evidence-based and effectiveness-focused care.

1.6.2 Dissemination for Patients and Caregivers

However, neither systematic reviews nor critical summaries serve to disseminate the best available evidence to the patient, stakeholders, and general lay public. To achieve that most critical step in metascience dissemination, it is timely and critical "to translate" the metascientific jargon into lay language. This is an important pillar of the greater, translational model of healthcare, which is the inevitable future. The ease of communication and understanding plays a critical role in services that aid a patient-centered approach, such as telehealth and its encompassing applications [8].

To be effectively used, the consensus of the best available evidence must be effectively disseminated. Systematic reviews, which can be arduous to read and comprehend, must be critically summarized in a clinician-friendly format and language and further produced in a lay-language summarized translation to aid patients, caregivers, and stakeholders to increase their health literacy. This is a major undertaking, which, although being central to the success and acceptance of evidence-based dentistry, is lagging substantially.

The evidence base for quality improvement interventions in dentistry is expanding more rapidly than our capability to disseminate this information effectively. The diversity of the initiatives and inconsistency in labeling of these interventions makes it a serious challenge for researchers, policymakers, and dentists to access the literature systematically to identify relevant consensus information and transmit the best evidence base to the interested parties.

Today, the weakest step in evidence-based clinical practice is the translation of the best available evidence findings to the patients and the stakeholders. In large part, the reason for this void is that no system of validation for such translations has yet been developed, standardized, validated, and widely accepted in the field.

1.7 Biases and Fallacies in Clinical Decision-Making

There is a fundamental distinction between biases and fallacies. Biases are persistent and widespread psycho-cognitive tendencies that are detrimental to maintaining our objectivity and rationality as we evaluate research and clinical evidence.

Fallacies, by contrast, are mistakes of reasoning: that is, errors of inductive or deductive judgment as opposed to mistakes that arise from facts. Both biases and fallacies impair the objectivity of metascience, although by different mechanisms: the former by altering our views of the evidence by means of our judgment of the facts a priori and the latter by altering our ability to judge the facts a posteriori by corrupted inductive or deductive reasoning about the evidence.

1.7.1 Cognitive Biases

Certain among the principal biases that blunt our objectivity can be summarized as follows:

- Status quo bias. The consideration that the current state of affairs is optimal. It follows that anything different will be detrimental.
- Confirmation bias. The confirmation bias, as pervasive as it is in human affairs, is the tendency to look for and to pay greater attention to information that confirms our preestablished views and supports our own views.
- Availability bias. The availability of bias refers to the tendency human nature has to draw conclusion based on information that is proximally available, rather than searching for better, perhaps more conclusive evidence. It is heuristic in that it is an approach to problem-solving that relies on the immediacy and practicality of anecdotal evidence, rather than on the pursuit of optimal or rational solutions.
- Framing bias. The framing of a research question or interpretation of findings into a context of preconceived notions, and judgments and positions forged a priori—that is, before the data are in—limits the possibility to fairly consider other alternative solutions and decisions.
- Bandwagon bias. We speak of the bandwagon effect when judgment is impaired by our tendency to follow the topic-of-the-moment; the opinions, as unfounded as they may be, of the larger or the stronger group; and the views, as dystopic and inaccurate as they might be, of a leader bully.
- Anchoring bias. Anchoring refers to hanging on to an idea, thought, or solution that is based on unfounded facts or irrelevant information, but which we have espoused based on little, or no logic- or evidence-based grounds.
- Hindsight bias. The hindsight bias refers to our tendency to look back at past events and adjust our current worldview to accommodate the new situation into the I-knew-it-all-along model.
- Halo-horn bias. The halo effect refers to the tendency to consider positively a proposition proffered by a person viewed positively as a positive proposition based on a predetermined opinion of the person, rather than an evidence-based examination of the proposition proffered. The horn effect is its direct opposite: to consider negatively a proposition proffered by a person generally viewed negatively, without examining the proposition in and of itself.
- Dunning-Kruger bias. This bias manifests as one's gross overestimation of one's ability or knowledge at a given task or in each domain of knowledge. It is a form of illusory superiority, an inability to recognize their lack of ability, and a serious lack of reality contact fueled by narcissistic tendencies. It consists of the inability to evaluate one's competence or incompetence objectively consequential to a lack of metacognitive self-awareness.

1.7.2 Fallacies

Fallacies, by contrast, are errors of reasoning that yield faulty or deceptive conclusions from the evidence, by making it appear to be better than it really is. There are two principal types of fallacies, which then subsume several variants, as follows:

- Non sequitur fallacy. A non sequitur fallacy, also termed a formal fallacy, is one whose arguments form. It is illogical or unfounded. For example, an argument based on a view is taken for granted simply because it is the view that it most certainly or even probably just be so; the consideration that a decision must be wrong on the sole grounds that the evidence is considered to be in error (a consideration that may be biased, as noted in the preceding section), and the presumption that an outcome may be more believable simply because it appears to satisfy several preestablished conditions, as if satisfying multiple conditions makes a cause-effect more probable than an outcome satisfying a single one strong evidence-based condition.
- Argumentum ad infinitum fallacy. A proposition repeatedly restated with no end (ad infinitum), regardless of its inherent errors, contradiction, or counterarguments. This fallacy is often called nonformal because it proffers arguments that are fallacious for reasons other than structure and form but rather require examination of the argument's content that is in error or in contradiction with reality or evidence-based facts.

1.8 Implications for TMJ and Airway Disorders in Dental Sleep Medicine

A growing body of research has implicated airway disorders consequential to temporomandibular joint disorders in alteration of sleep. Emerging systematic reviews and evidence-based findings proffer important new perspectives on effective treatment interventions.

1.8.1 Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a serious health issue that affects children, women, and men of all age ranges. Due to the severe medical and dental complications related to the disorder, both medical and dental providers play a key role in diagnosing and treating OSA. Correct treatment and regular follow-up are critical to the success of managing the disease and preventing multiple medical comorbidities.

Dental oral appliance therapy is one of the most common forms of treatment for OSA. Recently, a review of systematic reviews on mandibular advancement oral appliance therapy for obstructive sleep apnea was completed to provide useful information for practicing dentists involved in treatment of OSA [4]. The primary database used was Medline, and the inclusion criteria was limited to reviews in

English, testing only represented adult patients and treatment with oral appliances. Twenty-seven articles were included in the study. The content of the 27 systematic reviews was further broken down into five categories. The systematic review and meta-analysis consisted of ten articles on comparison with other treatments; five articles on types of mandibular advancement oral appliances; six articles on the effects and side effects of mandibular advancement oral appliances; the consultation rate for follow-up at the Ichikawa General Hospital, Tokyo Dental College; and the consultation rate in literature. Two articles used were on the changes of the upper respiratory tract caused by this therapy. Lastly, one article was on a remotely controlled positioner.

The systematic reviews on comparison of dental sleep appliances (DSA) with other treatments always included nasal continuous positive airway pressure (CPAP). All the systematic reviews stated that CPAP was more effective than DSA with respect to the patient's apnea-hypopnea index (AHI), Epworth sleepiness scale, and quality of life. It was also concluded that CPAP and DSA are the two best conservative treatment options.

Due to a large variety of appliances on the market, further evaluation of the different types of appliances and their effectiveness is of interest to the treating dentist. In Sato and Nakajima's review, the two categories of appliances evaluated were fixed jaw appliances, and appliances which were upper and lower jaws were separated. Based on their review, it was unclear which appliance was best, leaving room for more research into comparing effectiveness of all appliances on the market. Specifically, testing appliances that are custom made versus stock and comparing appliances that can be titrated versus fixed would provide valuable information for the treating dentists when deciding which appliance would be most effective for their patient. Comparing the long-term adherence of the different types of appliances would also be of benefit to the treating dentists when determining appliance for their patient. The review also indicated when fabricating the appliance, there was no standard starting position for the lower jaw that fits all patients. Studies that help determine ideal initial mandibular starting positions and techniques for titration of the device will greatly improve implementation and effectiveness of appliance therapy.

Of the articles reviewed, the investigators concluded that DSA did have a favorable effect on decreasing blood pressure. Some of the articles reviewed indicated that DSA was as effective as CPAP with regard to blood pressure but the time frame of the study was short. Further long-term observational studies would help determine if in fact DSA is effective at decreasing blood pressure, as well as exploring other effects of DSA therapy on overall health. The authors noted that while positive benefits did occur with DSA therapy, there were side effects of appliance use. They noted morphological changes in teeth and the skeleton, specifically the development of open bites. Such occlusal and joint changes due to the appliances are significant, and unfortunately many patients of the studies were not informed and made aware of the possibility of these side effects. It is critical that dentists properly inform their patients prior to start of treatment as some of the side effects can alter function and create significant changes in the TMJ. Further research into side effects and

alternatives to appliance therapy should be completed to help avoid these negative outcomes.

Lastly, it is important for patients entering appliance therapy to understand the necessity of regular long-term follow-ups with the dentist and medical provider. Once the appliance is fabricated and the patient is free of pain, confirmation of effectiveness with sleep tests is necessary. Critical to long-term success is further periodic follow-ups. They provide opportunities for the dentist to adjust the device as needed and to manage developing side effects as much as possible. In the hospital setting, Sato and Nakajma (2020) found that one in four patients discontinued follow-ups in the first year. Further research into understanding the barriers to adherence to both use of the device and follow-up would help in the long-term success of the treatment. In agreement with Sato and Nakajma (2020), increased education of sleep medicine in the undergraduate and graduate level will help foster further collaboration and innovation in treatment and eventual prevention of OSA.

1.8.2 Obstructive Sleep Apnea and Cognitive Decline

In a large systematic review spanning over multiple databases (PubMed, Embase, Web of Science, Cochrane Library), and including 27 observational studies and over 69,000 patients, Bubu and collaborators [26] confirmed the association between sleep impairment and cognitive decline. The research synthesis design used stringent inclusion criteria, including the following:

- Need to have reported primary or secondary data analysis of findings presented in either observational studies or a randomized control trial, relating to any type of association between sleep disorders and cognitive impairment or Alzheimer's disease
- Need to have a form of explicit measure of cognitive impairment or Alzheimer's disease or objective measures of Alzheimer pathology
- Need to have a form of explicit or objective measures of sleep problems
- Need to have incorporated comparison group with and without sleep problems in cohort studies
- Need to provide sufficient data to allow for quantifying the measure of association of sleep problems with cognitive impairment or Alzheimer's disease

The authors extracted the data on the basis of study design, study population, exposure and outcome assessment, statistical methods and tests used, covariates, and the main results of the study. The studies were divided into three groups in terms of quality of the evidence (low quality, medium quality, high quality) using the Newcastle-Ottawa Scale for quality assessment [27]. Sleep disorders were then assessed using the International Classification of Sleep Disorders (ICSD-3, 2014). Statistical analysis of the data involved effect sizes of included odd ratios, hazard ratios, Pearson's correlation coefficient, beta estimates, and standardized mean differences. Effect size findings were transformed to a common index, which allowed

computation of mean of the effect sizes for each study across multiple outcome measures. Mean effect sizes serve to calculate the common unit of analysis, relative risk. Effect estimates for sleep durations between <5 and 6.5 h were pooled as a single estimate for sleep duration of <6.5 h across a wide patient population extending between 40 and 91 years of age. Inclusion/exclusion criteria determined that of the initial 2341 studies, only 27 were used in the meta-analysis for 52 effect estimates pooled into 25 relative risk estimates**.**

Findings revealed that the relative risks for individuals with the following sleep problems—poor sleep quality, short and long sleep duration, circadian rhythm abnormality, insomnia, and obstructive sleep apnea—had a combined outcome of a 1.68 times higher risk of developing cognitive decline and Alzheimer's disease compared to those without such sleep problems. The range of the relative risks from this data set ranged between 1.07 and 4.25.

Considerable heterogeneity among the articles prohibitively raised the variance. Nonetheless, these findings confirmed previous reports that demonstrated the relationship between sleep, circadian rhythms, and Alzheimer's disease [28] and cognitive impairment and obstructive sleep apnea [29].

1.8.3 Obstructive Sleep Apnea in Children and Young Adults

Obstructive sleep apnea syndrome, one component of pediatric respiratory sleep disorders that include simple snoring and the increased upper airway resistance syndrome, is prevalent and underdiagnosed in children and young adults. It is a disorder of breathing during sleep. It manifests as prolonged partial upper airway obstruction that is prolonged in time, as well as intermittent complete obstructive apnea that disrupts normal ventilation during sleep and normal sleep patterns. It can have profound harmful effects on the central nervous and the cardiovascular systems and may significantly metabolize neuromuscular tone and normal physiology of the growing and developing youngster. It often affects the ability of the patient to concentrate in school and learn and retain information; consequentially, obstructive sleep apnea syndrome typically leads to poor academic performance and to severe behavioral problems. Sleep disturbance is an important risk factor for the development of depression during adolescence and young adulthood. Many factors favor the onset and exacerbation of obstructive sleep apnea syndrome, including adenotonsillar hypertrophy, overweight and obesity, craniofacial abnormalities, and stomatological neuromuscular disorders [30, 31].

Henst and collaborators [32] established the relationship between sleep extension interventions on cardiometabolic risk in young adults by means of a systematic review. A total of seven studies emerged from the inclusion/exclusion criteria of the analytical framework, with a total number of participants of 138, categorized as healthy ($n = 14$), healthy short-sleeping ($n = 92$), overweight short-sleeping ($n = 10$), or pre- or hypertensive short-sleeping ($n = 22$) individuals. The intervention duration across the studies ranged from 3 days to 6 weeks, and total sleep time was increased by between a minimum of 21 min and a maximum of 177 min. Clinically

relevant findings overwhelmingly indicated that sleep extension improved cardiometabolic physiologic parameters, from insulin sensitivity to decreased leptin, overall appetite, desire for sweet and salty foods, intake of daily free sugar, and percentage of daily caloric intake.

A recent study reviewed existing systematic reviews on the use of oral appliances by clinic-based dentists for treating airway disorders and consequential sleep impairment [4]. The compiled clinical evidence comprised systematic reviews of the effect of mandibular advancement of oral appliance. The findings suggested that there remains little evidence supporting the proposition that the use of mandibular advancement of oral appliances can effectively prevent cardiovascular disease or improve cardiometabolic development in young adults. The principal caveats of these conclusions were, nonetheless, the issue of lack of compliance of wearing such appliances and discontinued consultations. The nature of the limitations highlighted by this report strengthens the need to define and characterize the use and limits of systematic reviews in evidence-based clinical decision-making, particularly in the context of dental sleep medicine.

1.9 Conclusion

Metascience in dentistry and medicine translates to and is a well-grounded translational healthcare. It consists of two primary dimensions as follows:

- Translational research pertains to the process of ensuring the most up-to-date patient-centered clinical intervention by generating and interpreting the physiologic profile of the patient's laboratory that in turn informs the clinical decision-making process.
- Translational effectiveness relates to the process of judiciously integrating the best evidence base in the clinical intervention, taking in full account the patient's oral and medical condition and history, the clinician's training and expertise, and the patient's treatment needs and preferences.

Therefore, metascience in dentistry and medicine has both a research and a clinical aspect that are intertwined to ensure not only its patient-centeredness but also its efficacy, effectiveness, and efficiency. Evidence-based healthcare, in all domains of dentistry and medicine, including dental sleep medicine, is one of the major components of translational healthcare not only because recent advances in the field have established the intimately intertwined dependence between oral health and systemic health—including, as noted in preceding sections, sleep—but also largely because it seamlessly integrates translational research and comparative effectiveness research with the ultimate goal of optimizing evidence-based clinical care.

There is an important distinction between evidence-based healthcare and healthcare that is based on the evidence: the latter describes the attention and care that clinicians have for integrating the latest research advances into clinical practice.

Such is a laudable dedication on the part of the clinical sciences, but it suffers from several of the biases and fallacies discussed above.

By contrast, evidence-based healthcare is grounded on the systematic examination of the level and quality of all the available evidence by means of the metascience approach described in this chapter. It is the process of incorporating the consensus of the best evidence base into the decision for clinical intervention. It involves increasing the knowledge base, understanding, and health literacy of the patient and other stakeholders and their active involvement in patient-centered clinical decisions for treatment. It is the clinical model for the remainder of the twenty-first century in the treatment of temporomandibular joint and airway disorders, in dental sleep medicine, and more generally in healthcare.

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