Evidence-based endodontics

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This review defines evidence-based practice and discusses how the concept has been applied to endodontics. The focus is on treatment procedures in endodontics. The means used in the process and how far our knowledge base has reached are addressed. Aspects are also conveyed as to what future research in clinical endodontics should take into account.

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Background

Introduction

Diagnosis and treatment of the disease conditions of the dental pulp and the periradicular tissues are the primary focus of endodontic therapy. Over more than 100 years, clinical experience and scientific research have generated a substantial base of critical knowledge. Reports published in journals and textbooks, further analyzed in meetings and congresses, have indeed established the principles for endodontic therapy by outlining the biology of the dental pulp and periradicular tissues, the etiology and pathophysiology of the disease processes, and the measures to diagnose, prevent, and cure the different disorders. Case reports, case series, and reviews have also been published in an effort to assess how effective these procedures are in the practice of endodontics.

In more recent years, the development of what must be regarded as a new model for evaluating clinical procedures has emerged in our area, namely that associated with evidence-based medicine/dentistry. Over the past 15 years, numerous so-called systematic reviews have been published and created a new way to analyze and evaluate the effectiveness of the clinical methods of our discipline.

Evidence-based medicine is “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” This well-known definition emanates from the highly cited report published by David L. Sackett and collaborators in the 1996 British Medical Journal (1). It is a short, 1½-page-long article, given the title, “Evidence-based medicine: what it is and what it is not.” When this review was written, the report had over 3,500 citations in the Science Citation Index, which is very far beyond what any endodontic publication has recorded.

While evidence-based medicine/dentistry is concerned with the efficacy of the clinical procedures that we apply to treat our patients, the essence of the concept has not always been generally agreed upon. Even misunderstandings and accusations have been aired over the years. In fact, some regard it to be a pretentious way to value research that is completely unrealistic and serves to suppress clinical freedom and to enhance mechanisms that strive to reduce costs for patient care. However, during recent years hundreds of books and thousands of articles have been published on the concept. In addition, websites and various other channels of information issued by researchers, clinicians, and organizations have been released on this new paradigm in the clinical practice of health care including dentistry.

The current review focuses on the essence of evidence-based medicine/dentistry and how it has been applied to our discipline. Specifically discussed are the means or tools that are available to assess how well procedures, with a particular focus on treatment procedures in endodontics, have been achieved. We also gauge how far we are in our evaluations of what can be regarded as the best clinical evidence in
endodontics and finally propose key concepts for consideration in future research.

Evidence-based practice

Evidence-based practice is about the best available clinical evidence from systematic research and how it is integrated in the treatment of individual patients (Fig. 1). Sackett et al. (1) see two important parameters in the process. One is the individual clinical expertise, which is about “proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice.” The other is the best available external clinical evidence. It stems from patient-oriented research, when it is centered on “diagnostic tests, prognostic markers, and the efficacy and safety of rehabilitative and preventive regimens.” In other words, research for evidence-based practice is on clinical methods for patient care and how effective and safe they are when applied in a single clinical case.

In endodontics there are many relevant questions that apply. Take for example a situation when a patient is seeking care for pain. The tooth has deep caries, is tender to percussion, the pulp vitality test is negative, and an intraoral radiograph shows periapical radiolucency. The diagnosis is likely to be a necrotic pulp with apical periodontitis. The patient may ask:

- How sure are you on the diagnosis?
- What will happen if the condition is left untreated?
- What different treatment options do I have if I decide to go along with treatment?
- Will symptoms disappear?
- How does the disease and treatment affect my risk of losing the tooth?
- Is there a risk of persistence or relapse of disease?
- What will happen if this is the case?
- Would it be better to take the tooth out and replace it with an implant?

As a dentist caring for patients with this problem, one must respond to these questions and use them to guide the course of action. If your deliberations result in a decision to perform root canal treatment, there are also important questions for the professional such as:

- Should a one- or two-visit treatment be carried out?
- What type and concentration of disinfecting irrigation solution should be used?
- Which method and type of instrumentation is optimal?
- Which root filling material will give the best results?
- What type of permanent restoration will ensure long-term survival?

Clinical expertise

The article by Sackett et al. (1) emphasizes that neither individual clinical expertise nor the best available external evidence works very well alone. Without clinical expertise, patient care will suffer. And without the best external evidence, clinical practice easily becomes out-of-date and treatment efforts will go beyond what in modern days is considered adequate. Sackett et al. (1) express it in the following way: “External clinical evidence can inform but never replace individual expertise and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision.” It is thus important to understand that evidence-based dentistry is not just about applying scientific results to clinical practice. As a matter of fact, it combines the best scientific evidence with the operator’s clinical expertise and patient’s choices under which clinical treatments will be decided (Fig. 2).

It is important to recognize that there are different forms of skills a good clinician must acquire, not all of which can be learned from systematic research. One example is the technical skill a clinician must gain in
order to render proper treatments. Performing an adequate access cavity and identifying and instrumenting thin and severely curved canals are just a few examples of the skills a clinician must develop that only partially can be gained from research or “reading.” Therefore, attending practically focused workshops, watching other dentists at work, performing the procedures oneself (on models and patients), and reflecting on what has been learned from the failed cases are consistently important for the development of a skillful clinician.

The clinical situation also demands that the dentist exercises good clinical judgement. This means “to do the right thing at the right moment.” In the tradition of the works of the Greek philosopher Aristotle, the ability has been termed *phronesis* and can be translated to “practical wisdom.” It is concerned with how we make decisions in one way or another. All of this means that evidence-based practice is not just limited to proper clinical studies including randomized controlled studies and meta-analyses. It is about tracking down the best external evidence that exists to answer the specific questions that may occur in a given clinical case. It can therefore be concluded that in dentistry, including endodontics, proper clinical care is not only based on clinical research but also on the practical skills of a craftsman, where clinical and moral judgements are integral components.

**Needs and preferences of the patient**

The list of publications on patients’ preferences and quality of life aspects of our treatments in endodontics is far from exhaustive, even though some studies in recent years have focused on these issues (2–4). Besides the need for research on the outcomes of endodontic treatments, it must be recognized that preferences in a given clinical situation must be based on the patient’s views, as the interpretation will vary among patients. Only the patient is the expert on how he or she feels about maintaining a tooth with or without endodontic treatment, which symptoms are tolerable, which risks are worth taking, and what costs are acceptable.

As in all other health services, social development has led to the conclusion that we see the patient’s right to autonomous decision-making as an integral part of dental care. Procedures for obtaining informed consent play a key role in safeguarding this right. In the context of endodontics, informed consent means that the patient, after being given information about the relevant aspects of the clinical options, will determine whether or not to go ahead with the suggestions given by the clinician.

**Methods for clinical research**

Scientific research provides “evidence” which is defined as “the available body of facts or information indicating whether a belief or proposition is true or valid” (5). The assessment of clinical procedures can be carried out in a number of ways. Within the concept of scientific research, “bias” is the term for a process at any stage of inference tending to produce results and conclusions that deviate from the true condition systematically.

Evidence-based medicine/dentistry seeks to prioritize information in a hierarchy of evidence by study design from the most biased to the least biased. Knowledge about the biology of disease, *in vitro* studies, and studies on models, cadavers, or animals are certainly valuable here. Yet this kind of research does not, even if skillfully performed, take into account the realities of patient care including:
- the role of chance;
- the complex biology of human beings;
- patients as human individuals; and
- the interaction between doctors and patients.

Consequently, the usefulness/role of studies other than clinical ones will be limited and sparsely contribute to evidence-based answers to clinical issues. Unsystematic and anecdotal clinical information also
belong to this least valid form. Although anecdotal information is quite popular in the medical and dental fields, it is highly biased and impossible to verify and therefore carries limited value in determining treatment efficacy.

Case report

A simple method of clinical research is the description of clinical cases, which may show unique or unusual features of a disease or outcome of therapy. Such case analysis can occasionally be seen in our endodontic journals. It is the only means by which specific or even unexpected clinical events can be described and therefore important as further examinations may thus be initiated. The limitation of case presentations is, however, that evidence on efficacy, outcome rate, and prognosis cannot be transmitted.

Case series

Series of cases are more common and may provide better information. They are usually retrospective but may be prospective. Larger groups of patients with a particular disease or condition subjected to treatment are studied. These studies can determine the involvement of chance by statistical analysis. Yet the efficacy of the tested clinical procedure cannot be ascertained and certainly not be proven better or equal to any other method due to the lack of a control group. Inclusion of data from prior studies or other authors’ results may sometimes be used for comparison purposes (historical data). However, this procedure will not bring particularly strong evidence to the report as the conditions under which the studies were conducted were not equal. In essence, case series represent more tentative than conclusive observations. Hence, case studies and case series are best utilized to develop hypotheses rather than for testing hypotheses. If case series are sufficiently large then they may be used to document adverse effects of treatments that in other contexts have been shown to be effective.

Case-control study

Case-control studies also belong to the arsenal of methods for clinical research in endodontics. Although frequently used in the medical field, we have seen very few such studies in endodontic journals. In a report by Shafiei & Shahravan (6) examining the character of papers published during 2000, 2006, and 2010 in our two most recognized endodontic journals, the International Endodontic Journal and the Journal of Endodontics, only seven such papers were identified. In a case-control study, the starting point is the already-known outcome of treated cases and it goes back to search for exposures (contributing or causative factors) to the outcome. Hence, in endodontic research the influence of an exposure, for example the presence of bacteria at the time of the root filling in a matched series of cases, can be examined. The test group would then be cases with lesions at follow-up and the comparison group or reference group, treated cases without lesions at follow-up.

Case-control studies are less costly compared to prospective cohort studies (see below). They are fairly easy to conduct and require shorter times for data collection. A significant drawback is the difficulty in obtaining critical information about the exposure status over time. It is also difficult to find a good control group in these studies and selection bias is therefore always a concern (see further below). Recall bias is another common problem (see also below). All of this causes the case-control study to be placed fairly low in the hierarchy of evidence for clinical research. It is thus ranked after RCT and prospective cohort studies, but before case series and case reports (Fig. 3).

To provide good evidence, clinical research requires being prospective. Important features are proper control procedures and monitoring of parameters of significance to the outcome. Retrospective studies of any nature will therefore not do well as they suffer the risk of having limited or no control of a number of aspects relevant to the outcome. This includes, for example, a most important aspect, namely the number of the original set-up of patients who were seen at follow-ups.

Prospective cohort study

A type of clinical research design that should be used more often in endodontics is the prospective cohort observational study. Given that a comprehensive registry of patients under treatment currently is underway in many countries, valuable information on the efficacy of clinical treatment protocols can be gained. This study design means that dentists can clinically work in their normal manner. A large sample
of patients can then be assembled for follow-up examinations. Treatment protocols assigned to different clinics can furthermore be used for comparison purposes. Follow-up times must be set and patients checked on a regular basis.

An important factor of such studies is that a fairly large number of clinics have to be included in order for the report to gain generalizability. That aspect may be a difficult and costly item. Agreement must also be reached on the protocol for the procedure to be tested. But the study design has the advantage of allowing the inclusion of general dentists and therefore may reveal aspects of endodontics of which we have very little understanding. A problem is that these studies are expensive, time-consuming, and require careful attention to detail. Regardless of the care taken to choose the control group, selection bias is always a concern. Cohort refers to a group of patients, and cohort studies are a type of observational study using a comparator.

**Randomized controlled trial**

Randomized controlled trials (RCTs), unlike the preceding study designs, are true controlled experiments. Two or more groups of subjects receive different interventions and are followed forward in time and at some point are compared using an outcome measure. This kind of study observes the effect of only a single variable (Fig. 4). All other variables (background variables, confounders) are then maintained in both the test and the control group. An important feature of RCTs is that patients are allocated to test and control procedures in a strictly randomized manner. To be appropriate, an RCT also requires a pre-calculated minimal number of patients to be included in order to ensure that a statistical difference between the test and the control procedure can be ascertained. However, this estimate can be difficult to determine and may best be calculated if some prior knowledge exists on the potential outcome of the treatment.

RCTs are indeed powerful tools as many of the biases that affect non-randomized trials can be eliminated. Yet we have not seen many such studies in our discipline over the years. As a matter of fact, in the exposure of the type of studies published in our two major endodontic journals, Shafiei & Shahravan (6) identified only 3.7% of all published endodontic articles as RCTs. However, there was a slight increase from 8 publications in the year 2000 to 44 in 2010. Nonetheless the number is still low. A contributory factor to the low publication rate of RCTs is the long time they require to conduct. There are also high costs involved. Careful planning is therefore required and good training of the operators and continuous control of the procedures in both the test and control groups must be maintained.

On careful consideration, we must realize that RCTs may not attain evidence-based research very easily for clinical endodontics. In fact, RCTs are ideal for testing the effects of drugs because they can use placebos and
be controlled double-blinded. However, for the assessment of surgical interventions such as endodontic procedures, several predicaments occur. For example it is often impossible, even after proper randomization, to perform the study without knowing how the treatment option was allocated. A typical example here would be an RCT comparing root canal treatment to extraction and placement of a single dental implant. It is likely that the values and expectations of the patients, the dentists, and the evaluators could influence the assessment of the outcome in a biased way. Deviations from an ideal RCT must always be justified and inevitable (7).

Also when patients and evaluators are blinded to the allocated treatment, interfering background variables may occur. These include for example teeth with a different infection status, irregular difficulty in accessing the pulp chamber, number of roots, variable root canal anatomy, and the length and character of the disease process both clinically and histologically. All of these confounders are indeed difficult to balance in the test and control procedures. This means that different RCTs investigating a given clinical question may arrive at different conclusions depending upon the setting for the study. A good example from the literature is the RCTs on the effect of root canal sealers carried out by Eriksen et al. (8) and Ørstavik & Hörsted-Bindslev (9). It was noted in the first study conducted in Oslo that chloropercha had a slightly but significantly worse outcome as a root canal sealer than did AH 26 and ProcoSol. When the same study was carried out in Aarhus a few years later (9), no such difference could be noted and chloropercha performed equally as well as AH 26. It was revealed that the overall treatment results were worse in Aarhus, which could have influenced the outcome of that study. It was also inferred that marked differences in the preoperative diagnoses and in the technical problems associated with the teeth selected for treatment may have been different in the two studies. Thus it must be emphasized that a single RCT (even if meticulously conducted) may not be sufficient to provide good evidence.

**Systematic review**

Systematic reviews are a special type of review article that can be considered to provide the highest level of evidence when several similar randomized controlled trials on the same clinical question are utilized. Systematic reviews, unlike textbook chapters or narrative reviews, require careful planning and inclusion of methods that minimize bias and random error. The methods must then be transparent in order to allow other researchers to replicate the results and reach similar conclusions.
Meta-analysis

Meta-analysis is a specialized type of systematic review where data are pooled for a quantitative rather than a qualitative analysis. This type of study can provide the highest level of evidence if the report is limited to proper randomized controlled trials. Meta-analysis may, however, include studies of lower levels of evidence and can for this reason not be regarded as a high level of evidence. If for example case series were included there is a risk of including repeated systematic errors, which may give the review an even more biased angle than single studies.

Assessing evidence-based research

The PICO concept

In assessing the scientific quality of individual RCTs, a number of factors are essential. These aspects sum up into an account of internal validity (the degree to which the results of a study are correct for the sample of patients being studied) and the extent of external validity (generalizability) (the degree to which the results of an observation hold true in other settings) (see also Fig. 5).

A good starting point to use for evaluating the quality of an RCT is the PICO concept. This stands for population, intervention, control procedure, and outcome measure. The PICO model can also be adopted for other types of studies, both for planning as well as for evaluating individual studies in, for example, a systematic review. However, at each “letter” there are many pitfalls that must be avoided if the study is to produce results of high internal and external validity (Fig. 6). PICO helps the researcher or evaluator to systematically evaluate all of the phases of a study.

Biases in clinical research

The quality of studies is subject to the risk of being limited by numerous biases. The problem affects all kinds of reports including the top articles in the evidence pyramid (prospective cohort studies and RCTs). Biases are in four wide-ranging categories, viz. sampling bias, selection bias, measurement bias, and confounding bias (10).

Sampling bias arises when the sample of patients is systematically different from those suitable for the research question or the clinical use of the information. For example, studies on the outcome of root canal treatment are often conducted in dental schools or specialist centers. An important question is are these teeth representative of “teeth with necrotic
pulps and apical periodontitis” in general? Perhaps are teeth that would be treated in general practice discharged from the study preoperatively? Or is the contrary in effect? When reporting a clinical study, it is always important to accurately describe the inclusion and exclusion criteria for the subjects included in the study.

Selection bias arises when comparisons are made on groups that differ in ways other than the factors under study. Groups of patients often differ in many ways by age, sex, general health, and severity of disease. If we compare the outcome of two groups that differ on a specific issue of interest (for example one- versus two-visit root canal treatment) but are dissimilar in any other way and this difference itself is related to the outcome of interest, the comparison between the groups will be biased. Thus little can be concluded from the results. In our example of one- versus two-visit endodontic treatment, if “easy cases” (perhaps premolars and incisors) are more frequent in the one-visit group, the outcome may be systematically better, or poorer. Randomization is the best way to overcome these difficulties. The randomization procedures must then be performed without manipulation and be clearly described in the methods of the study.

Measurement bias arises when the means or methods of measurement are different among the groups of patients. This is the reason why historical comparisons (data from other reports) often are invalid. In endodontics, where analysis of radiographs plays an important role in comparisons between groups, all patients must be examined with the same radiographic method. Results from a study where intraoral radiographs were used should therefore not be compared with a group of patients examined with cone beam computed tomography (CBCT). Another problem may be the lack of common criteria for evaluating the outcome. For example, when comparing results of non-surgical and surgical endodontic procedures, there is no mutually recognized way to interpret “healing” from “no healing” in radiographs. The problem with intra- and inter-observer variation must also be handled in an appropriate way by using blinded and independent evaluators. The authors of a research article must therefore give a proper account of these matters.

Confounding bias arises when two factors are associated with each other and the effect of one is confused with or distorted by the effect of the other. For example, if the survival of a group of teeth that had

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Fig. 6. The PICO concept applied for a fictive RCT on one- versus two-visit treatment of teeth with necrotic pulp and apical periodontitis.
surgical retreatment is compared with a group where non-surgical retreatment was conducted, perhaps the result showed a significantly higher survival after 10 years in the non-surgical retreatment group. However, further analyses of the data may reveal that in the non-surgical group a new crown was placed more frequently postoperatively than in the surgical group. Consequently it may be that the placement of the new crown rather than the choice of treatment explained the observed difference in outcome.

**The influence of chance**

The observed difference between the intervention and the control group in a clinical study cannot be expected to represent a true difference because of the random variation between the groups being compared. Statistical tests help to estimate how well the observed difference approximates the real difference.

There are two main approaches in assessing the role of chance in clinical studies, hypothesis testing and estimation. With hypothesis testing, statistical tests are conducted to calculate the probability that the observed result was by chance. This calculation may result in both false positive and false negative statistical errors. A Type I error relates to the conclusion of an effect of the tested procedure that does not exist in reality, while a Type II error means that there is a positive effect which the data failed to show. The acceptable size of the risk for errors of both types is a value judgement. It is customary to set the risk for Type I errors at 1% or 5%. For Type II errors, a considerably higher risk of error is normally accepted and the probability is usually given at 20%.

In order to avoid statistical errors, sample size is an important concern. A calculation (“power analysis”) should therefore be carried out prior to the onset of a study in order to analyze how many patients are needed to avoid a Type II error. Generally speaking, in order to obtain statistical significance, more patients must be included in the study if differences are small than in situations where large differences occur. However, even when a proper “power analysis” is respected in the implementation of the study, researchers take the risk of being mistaken every fifth time a study does not show a statistically significant difference (Type II error 20%). But if a statistically significant difference is found, the risk of being mistaken is only one (Type I error 1%) or five (Type I error 5%) in a hundred instances (Fig. 7).

These potential errors in hypothesis testing have made many researchers and statisticians prefer estimation statistics (11). This type of control for chance uses the data to define the range of values that is likely to include the true effect. Point estimates (the observed effect) and confidence intervals are used here. They emphasize the size of the effect and not the p-value as well as show the range of plausible values (Fig. 8).

**Statistical and clinical significance**

It is important to realize that statistical difference only tells if the difference observed is likely to be true, but
not that it is important or large. In clinical research it is therefore highly important to clarify the distinction between statistical and clinical significance. Even with a small p-value (the risk of a Type I error), the difference is not necessarily clinically important. In fact completely trivial differences in well-designed studies may be highly significant on a statistical level if a large number of patients were studied, but the difference may be clinically of little or no relevance. However, a high p-value can occur even for a large and important difference between groups if only a few patients were recruited for the study.

**Loss to follow-up**

A serious problem in modern clinical endodontic research is the loss of patients to follow-up. Numerous examples exist in our literature where the control group became too small to be statistically valid because too many patients were unable to attend the follow-up visit for the tested procedure. Short follow-up periods of 1 and 2 years may do well, but once extended, patient losses increase and the results can easily become invalidated. Thirty percent is a common figure used as the highest loss of patients for recall in a study to be included in a systematic review. However, while 5- and 10-year follow-up data are highly desirable, few, if any, studies have been published in our field that reach this high number of attendance. Losses of patients may be due to various reasons. A most important reason, which normally cannot be checked, is that the treatment failed and resulted in a decision by the patient not to attend the recall.

**Clinically relevant outcomes**

Because of their selection and training, dentists in general and scholars in particular tend to prefer the kind of precise measurements the physical and biological sciences provide; they discount others, especially with respect to research. In endodontics, there are numerous studies concerned with the maintenance of pulp vitality, formation of hard tissue repair, elimination of microbes, quality of root fillings, and disappearance or reduction of periapical radiolucencies. Yet relief of symptoms, retaining a functional and asymptomatic tooth in the long term, and a feeling of well-being are among the important outcomes of dental care. These are central concerns of patients and dentists alike. To guide clinical decisions, reports of clinical research should therefore always include these basic patient-centered outcomes.

**Surrogate endpoints**

Outcome measures that do not carry direct practical importance but are believed to reflect genuine outcomes are called surrogate measures. They often include physiological or biochemical markers that can be relatively quickly and easily measured and taken as being predictive of a true clinical outcome. Surrogate endpoints are often used when the observation of clinical outcomes requires long-term follow-ups. However, it is important to remember that there must be a good reason to accept a surrogate endpoint. It is critical that the correlation of the surrogate with the clinically important endpoint be well established. For example, root canal sampling and results of culturing were used as a surrogate endpoint in clinical trials for a long time in endodontic research. But these types of studies have recently been criticized for several now-obvious reasons. In light of the increasing knowledge of the complexity of the microbiological biofilm present in infected root canals, the difficulty of its eradication, and the results of molecular genetic identification techniques, the relevance of microbial root canal sampling and culturing has been questioned (12). Furthermore, clinical follow-up studies have only partially been able to establish a correlation between the results of sampling and culturing with asymptomatic teeth and healing of apical periodontitis, the true clinical endpoint measure.

**Efficacy and effectiveness**

Results of clinical studies must be judged in relation to two broad questions. Can the diagnostic method or treatment work under ideal circumstances? Does it work in ordinary settings? The terms efficacy and effectiveness have been applied here. It may be a question of the dentist’s experience, ability, attention to detail, meticulousness, and skill. It is seldom possible to assess the extent such factors influence the results in treatment studies and clinical evaluations. It is, however, reasonable that in a clinical discipline such as endodontics, these factors are important because of the technically complicated nature of many procedures. In molar endodontics in particular, the
diagnosis and treatment is often complex and the influence of the operator on the results cannot be overvalued. So far, most clinical studies in endodontics have been conducted in academic or specialist settings (efficacy) where devices that substantially facilitate the technical procedures are widespread and will affect the outcome rate. For the future, it is important that clinical research is also conducted to explore how endodontics does in general practice, where the majority of endodontic procedures are performed (effectiveness).

Publication bias

Dentists and researchers prefer good news. It is much less appealing to author and publish an article where the results are disappointing, negative, or perhaps much worse than previously published, than to describe successful treatments. It must be realized that research projects which attain publication status are a biased sample of all research being conducted. Hence, it is not unreasonable to assume that our inclination for “good” and positive results leads to a biased publication of articles. For example, imagine a group of clinicians who have performed an excellent study from a methodological point of view about endodontic surgery but they had a healing rate of 50% in both the intervention and control group. With what degree of enthusiasm will the writing of this article begin? What will the reaction of journal editors and reviewers be if the article was written and submitted?

The level of evidence for systematic reviews

There are several approaches to summarize the scientific basis for clinical practice. In recent years, with thanks to developments in computer and IT technology, large amounts of data and literature can be both searched and retrieved within a very short period of time, and so-called systematic reviews have become increasingly common. By definition, the review must be conducted in a systematic way and contain at least these four components:

- Formulating a clear question (or several clear questions).
- Searching and identifying relevant research.
- Collecting and critically analyzing included reports.
- Summarizing results, making conclusions, and giving recommendations as to how to proceed in the clinical setting.

Some systematic reviews are comprehensive and try to cover a complete clinical specialty, such as endodontics. One example is the report by the Swedish Council on Health Technology Assessment (SBU, 13). SBU is a national government agency that assesses healthcare technologies. A thorough review of the methods that we use to diagnose, prevent, and treat inflammation and infection of the dental pulp and the periapical tissue was performed and published in a 515-page book.

At the other end of the spectrum are systematic reviews that only seek to answer a single specific clinical question. For instance, the Cochrane Institute has published systematic reviews relevant to endodontics concerning, for example, surgical versus non-surgical retreatment (14), one- versus two-treatment visits (15), and irrigation (16). By evaluating only studies on one question at a time, the Cochrane reviews strive to perform a statistical meta-analysis when possible. However, very frequently these studies lack enough evidence for a clear clinical recommendation.

Systems for quality analysis of systematic reviews

Systematic reviews may be more or less stringent as to which studies were included and reports may appear that are lower-ranked in the evidence pyramid. Cochrane reviews allow only RCTs in their reviews while for example SBU also includes prospective cohort studies. Systematic reviews published in dental journals, including endodontics, do not always apply an equally strict approach.

A number of approaches have been used to evaluate the levels of evidence and strength of recommendations of systematic reviews but no consensus has been reached. Each one may be affected by a number of shortcomings (17). The SBU and several other institutions for Health Technology Assessment (HTA) use the GRADE system to summarize the strength of the evidence on each particular issue being assessed (18) (Fig. 9).

Systematic reviews and meta-analyses have become increasingly important in guiding healthcare policies. Dentists are interested in reading these reports to
update their field and may also use them for starting or changing clinical practice guidelines. As with all research, the value of a systematic review depends on what was done, what was found, and the lucidity of the report. Consequently, a systematic review must be exposed to quality checks similar to any other publication in clinical research. For example, meta-analyses must show clarity on the lengths of follow-up periods. Also sensitivity analyses, to illustrate whether choosing different endpoints affects the results, is an important feature in the evaluation of the quality of a systematic review. Protocols for analyzing the relevance of systematic reviews have been developed and may also be used by clinicians before implementing the conclusions of the reviews into their clinical practice (19,20).

Current knowledge base in endodontics

Unfortunately, in recent years, several careful analyses of the scientific basis for the methods we apply in endodontics have demonstrated extensive shortcomings (13,14,21–34). The situation is worrying for diagnostic and treatment procedures as well as for the assessment of the results of our methods. It is generally acknowledged by the profession, the patients, and the dental societies that practitioners have gathered lengthy clinical experience and that results from *in vitro*, animal, and clinical studies provide a basis for understanding how the pulp and the periapical tissues respond to therapeutic interventions. Certainly, many clinical investigations have confirmed that an inflamed pulp can be successfully treated with a conservative procedure. Yet, to date there is no analysis available of the presenting clinical conditions regarding which cases are likely to respond well, and which treatment measures will render teeth functional and asymptomatic. Many follow-up studies have also demonstrated that teeth with necrotic and infected pulps can be treated endodontically to achieve a healthy outcome that can last for many years. This bulk of knowledge has repeatedly been presented in scientific journal reviews and textbooks of endodontics. However, there are few clinical studies of high scientific quality. Consequently, there is a lack of scientific evidence to show which treatment protocols are the most effective and result in root-filled teeth with minimal risk of recurrent symptoms, periapical inflammation, or tooth loss. The fact that there is in general no specific scientific basis for the selection of methods for diagnosis and treatment in endodontics does not imply that there are no grounds for considering a particular method in routine clinical practice. In the concept of evidence-based medicine, the clinical expertise is based on three cornerstones. Within the concept of expertise lies the ability to implement ethical aspects. The following four principles, which are well established in biomedical ethics, are often presented as a basis for ethics in health and medical care (35):

<table>
<thead>
<tr>
<th>STRONG SCIENTIFIC EVIDENCE</th>
<th>BASED ON HIGH OR MEDIUM QUALITY STUDIES WITH NO FACTORS THAT WEAKEN THE OVERALL ASSESSMENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODERATELY STRONG SCIENTIFIC EVIDENCE</td>
<td>BASED ON HIGH OR MEDIUM QUALITY STUDIES WITH ISOLATED FACTORS THAT WEAKEN THE OVERALL ASSESSMENT.</td>
</tr>
<tr>
<td>LIMITED SCIENTIFIC EVIDENCE</td>
<td>BASED ON HIGH OR MEDIUM QUALITY STUDIES HAVING FACTORS THAT WEAKEN THE OVERALL ASSESSMENT.</td>
</tr>
<tr>
<td>INSUFFICIENT SCIENTIFIC EVIDENCE</td>
<td>SCIENTIFIC EVIDENCE IS DEEMED INSUFFICIENT WHEN SCIENTIFIC FINDINGS ARE ABSENT, THE QUALITY OF AVAILABLE STUDIES IS LOW, OR STUDIES OF SIMILAR QUALITY PRESENT CONFLICTING FINDINGS.</td>
</tr>
<tr>
<td>SCIENTIFIC EVIDENCE LACKING</td>
<td>NO STUDIES MEETING INCLUSION CRITERIA ARE AVAILABLE.</td>
</tr>
</tbody>
</table>

Fig. 9. The GRADE system is a tool for the assessment of the overall strength of the scientific basis for a specific clinical question. Each outcome is founded on the study design assessed in the overall appraisal. The strength of the evidence may thereafter be positively or negatively affected by the internal and external validity of the study. The stronger the evidence, the lower the probability that new findings will affect the evidence within the foreseeable future.
1. The do-good principle means that one should try to help the patient by satisfying the (medical and basic human) needs.
2. The do-no-harm principle means that one should avoid harming the patient. One should, for example, avoid taking unjustifiable risks.
3. The autonomy principle means that one should respect the patient’s right to self-determination, which implies that one must keep the patient informed and guarantee him or her the right to decline the treatment being offered.
4. The principle of fairness or justice means that patients with similar needs should be treated similarly. This means that it is the patient’s treatment needs which should determine the course of action, not for example the patient’s cultural background, gender, financial, or social standing.

Based on these four principles, the following advice seems reasonable (13):

- Methods that may expose the patient to great risks should be avoided.
- Methods that are particularly expensive should also be avoided until they have been proven superior in scientific studies.
- When evidence is lacking, preference should be given to diagnosis and treatment procedures that are supported by relevant established theoretical hypotheses until empirical support is available, rather than selecting methods which are not based on theory.
- In cases with a complete lack of evidence, clinicians should act in accordance with accepted guidelines for “good clinical practice.”

### Key areas for clinical endodontic research

A major concern of endodontics is to combat the infectious conditions of the root canal system of the teeth. Though doubted by many over many years, the evidence for the role of infection is today overwhelming and there seems to be an overall consensus, at least on a scientific level, that endodontic conditions in general have an infectious origination. Painful symptoms associated with pulpitis and bone destructions in apical periodontitis may yet be caused by something other than infectious insults at times. The focus of endodontic therapy is to prevent and combat the active growth of bacterial organisms in the root canal system of the teeth, while insults such as material toxicity and foreign body reactions may participate but not be critical to the attainment of successful treatment.

The introduction of molecular methods for the identification of bacterial species and the realization that advanced infections of the root canal system are mediated by microbial biofilms have increased our knowledge base substantially in recent years. Although we still have no solid data on the best clinical methods to eliminate root canal infections, our focus has never been so clear on the scope of identifying the means by which they can be eradicated.

While numerous ways exist to combat bacterial infections of root canals, modern endodontics is not just about antimicrobial effects and tissue toxicity but also how the dentin substrate of the root canal system may be affected by the procedures. It has recently been observed that common methods for root canal disinfection including the use of sodium hypochlorite may prevent the differentiation of pulpal stem cells to odontoblasts (36). This aspect has emerged because of the goals of regenerative endodontics and the potential to shape and organize new pulps in root canals that have lost their original pulps. Therefore we also have a focus on the disinfection procedures in that the prime objective of endodontics is not only to kill the infectious elements but to do it in such a way that it is possible for new tissue to regenerate.

Regeneration means restitution of the original tissue. So far no in vivo reports have shown that this is indeed feasible (37). Most often tissue originating from the periodontal ligament will penetrate but fail to form the features of the original pulp. Thus often a fibrous tissue is developed and bone tissue may come along that eventually might cause complications by merging with the inner root canal wall and possibly inducing resorbing processes.

A special area that has not received much attention in endodontic research is methods for the diagnosis of dental pulp conditions (13). Mejäre et al. (31) observed in a thorough review of the literature that new studies have rarely been published in recent years. As a matter of fact, only a few studies have been designed to assess the accuracy of tests or methods for the diagnosis of pulp and the extent to which it is broken down by necrosis. There are hardly any
systematic reviews available that have critically evaluated the scientific basis for the procedures which we commonly employ. It is especially critical to assess the condition of the pulp in teeth exposed to deep caries. Often the inflammatory process of the pulp is fairly limited as the infection has not extended very far. Thus the potential exists that frequently the tissue can be preserved either partially or totally. Yet there are no means available to decide how extensive the infection is and the extent to which the tissue is inflamed. Clinicians must rely on the occurrence of painful symptoms, depth of caries penetration, and possibly the character of bleeding. Therefore clinicians are often inclined to take what may be regarded as the safer pulpectomy procedure as opposed to trying the often considered riskier incomplete caries removal, pulp capping, or pulpotomy treatment. Some recent publications have challenged this approach and further research on these aspects of endodontics is considered of high priority due to the great number of pulps exposed by deep caries worldwide and limited resources that can at the same time be spent on conservative dentistry in many societies (38,39).

Overall a variety of specific questions exist in the treatment of endodontics and include the number of appointments issue, the impact of the level of apical instrumentation and filling, the significance of removing the smear layer, and the impact on the outcome of filling materials and techniques. While these aspects attract considerable interest, the SBU report in 2010 (13) identified a number of key elements that seem relevant from the healthcare perspective. These include the long-term survival of root-filled teeth, the factors that influence the loss of root-filled teeth, the extent to which root canal treatments will fail to achieve healthy outcomes and require further treatment, the risk that teeth with persistent but asymptomatic periapical lesions will lead to pain and swellings and/or increases in the magnitude of bone lesions, and finally the risk involved to general health by not intervening in cases of teeth with persistent apical periodontitis (see also 40).

Future directions

Most dentists, patients, and third party insurers would probably agree that endodontic research is important. But few consider that all research which is implemented and published is important. Resources for research including money, time, and supporting personnel are limited. Certain restrictions are therefore necessary. Yet what we want is good research. So what is good research? There is no clear answer to that question. However, there are at least three perspectives from which ideas for future research in endodontics could be assessed from a quality aspect (41):

- Is the research beneficial?
- Does the research meet scientific requirements for quality?
- Is the research ethically acceptable?

These three ways to recognize the value of good research can be combined in a number of ways. Research can at best be useful, impeccable, and ethical. At worst it can be useless, badly implemented, and unethical. For example, a study that examines the outcome of root canal treatment in general dentistry can be both useful and ethically correct. However, if the scientific methods are improper and maybe based on a retrospective study design, it may not be reasonable to conduct. Another example is a study that examines the natural history of teeth with necrotic pulps and apical periodontitis. If such a study were conducted in a scientifically optimal way, it certainly would be valuable to our discipline. Yet such a project is likely to fail ethical approval. A third example is a study that compares the effect of two different irrigating solutions. It could be scientifically exemplary and without ethical objections if planned and conducted well. However, if only a small difference of the concentrations is tested, the research project, given the light of present knowledge, would be of meagre clinical benefit.

Clinically oriented research projects in endodontics will have to meet all three criteria for “good science” in order to be competitive in the growing race for funding within dentistry and medicine. Good research will enhance our possibilities of obtaining support from institutions and other sources for our hard work and efforts and it will provide evidence-based endodontics for our patients in future clinical work. The alternative is to languish in a research environment where resources are scarce and the issues of research are uninteresting and trivial except to a very few.

References

Evidence-based endodontics


