Practical Application of Evidence-Based Practice

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KEYWORDS

• Evidence-based practice • Evidence-based medicine • Clinical epidemiology

KEY POINTS

- Evidence-based practice (EBP) is the integration of clinical expertise, client values and preferences, and best research evidence into the decision-making process for clinical care.
- Practical application of EBP involves asking well-focused questions, searching the literature for relevant research evidence, critically appraising the evidence, and applying findings to patient care.
- A high-quality evidence base is lacking in many areas of veterinary medicine. Practitioners must develop new skills to efficiently identify relevant evidence and examine its internal and external validity.
- Basic understanding of PICO question format, literature search strategies, and clinical epidemiology principles (chance, bias, confounding, and generalizability) are valuable to veterinary EBP practitioners.

Veterinarians desire to provide best-quality medicine to patients, and to counsel clients wisely during the medical decision-making process. Pet owners value our experiences and skills, but they also depend on us to provide care that reflects contemporary knowledge and standards of care. High-quality clinical practice requires veterinarians to be aware of new research and continually integrate relevant findings into patient care. Evidence-based practice (EBP) provides us with a practical framework to achieve this.

EBP is based on the principles of clinical epidemiology, the branch of medicine concerned with conducting, appraising, and applying research studies that focus on patients' medical care and disease outcomes.[1] A contemporary definition of EBP is the integration of clinical expertise, client (or patient) values and preferences, and best research evidence into the decision-making process for clinical care.[2] Clinical expertise is the veterinarian's knowledge base, skills, and personal experiences. Clients'

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values and preferences include their reasons for pet ownership, past experiences, financial resources, emotional attachment, and general medical knowledge. Best research evidence refers to research findings that are relevant to the individual and clinical scenario, and ideally based on sound scientific methodology.

A practical application of EBP involves the following steps:

- Asking a well-formulated question based on a real clinical case or problem
- Acquiring relevant research and information
- Appraising the strength and relevance of the evidence
- Applying the findings to the actual clinical scenario

For most clinicians, successful application of EBP will require developing new clinical epidemiology skills, specifically those related to appraising and interpreting research evidence.[3] This article gives particular attention to the appraisal step of EBP, with a focus on understanding and applying basic epidemiologic principles.

ASKING A QUESTION

The EBP process begins by assessing the patient and articulating a question or problem of interest. Not every patient problem requires a formal application of EBP. In many scenarios, effective diagnostic tests or treatments are established, prognosis for disease is known, or perhaps the client has no interest in moving forward. Relevant EBP questions arise when confronted with the following:

- Unfamiliar species
- Unusual clinical signs or test results
- Rare disease processes
- Common conditions for which there are multiple tests or treatments
- Conflicting recommendations and opinions

Once you have identified the clinical problem, the next step is to formulate a concise, specific, answerable question. A recommended approach is to build questions using PICO, a mnemonic that provides a structured, easy-to-remember formula for creating EBP questions (**Table 1**). A focused and specific question will facilitate the next step in the process, which is to develop a list of publications that are relevant to your clinical problem.

ACQUIRING INFORMATION

Research literature can be categorized into 3 main forms:

- Primary literature: original scientific articles that describe conduct and results of experimental and observational research
  - Aims to answer specific questions or test hypotheses
  - Original scientific journal articles peer-reviewed by experts
  - Difficulties and limitations: large volume; findings of different studies may conflict; rigor and validity of research varies; some topics are studied more than others
- Secondary literature: interpretation, analysis, and summary of primary sources
  - Aims to synthesize existing knowledge on a particular topic, using scientific (systematic) or nonscientific (narrative) methods
  - Textbooks, systematic reviews and meta-analyses, narrative review articles, knowledge summaries, editorials; often peer-reviewed or peer-edited by experts

Table 1
Guidelines for creating focused evidence-based practice questions using a PICO approach

PICO Component	PICO Component Explanation	Therapy Questions	Diagnostic Test Questions	Risk or Prognostic Factor Questions
*P*atient	The defining characteristics of the patient or problem	Example: species, condition, disease stage, clinical sign	Example: species, condition, disease stage, treatment	Example: species, condition, disease stage, treatment
*I*ntervention	The treatment, exposure, test, prognostic factor, or characteristic you want to understand	Example: medication type, dose, or regimen; surgical procedure, implant, or technique; diet; environment; order of combination treatments	Example: examination finding, blood test, clinical sign, imaging result, biopsy test or technique, survey response	Example: exposure to a toxin, environment, medication or treatment; species, signalment, body weight, stage; concurrent disease or clinical sign
*C*omparison	The main alternative to the intervention that you are considering	Example: no treatment; a different form of treatment; a different dose, brand, regimen, or order of treatment	Example: a different sign, finding, or test; often an existing test that is considered the gold standard	Example: not having the exposure, characteristic, disease, or sign
*O*utcome	The result you would like to prevent, cause, or measure	Example: cure or remission rate; test or imaging result; speed of recovery; side effects or complications	Example: identify presence or absence of disease	Example: development or progression of disease, clinical signs, complications, or other events

Example therapy question: In *guinea pigs with conjunctivitis*, do *oral* versus *topical* antibiotics result in a *faster resolution of signs*?

Example diagnostic test question: In *ferrets presenting with weakness and weight loss*, how accurate is a *single fasting glucose measurement* compared with *insulin-glucose ratio* for *ruling out insulinoma*?

Example risk factor question: In *pet aquatic turtles*, is *water temperature* $\geq 80^{\circ}F$ versus *less than* $80^{\circ}F$ a risk factor for *developing shell rot*?

  - Difficulties and limitations: authors and editors can introduce personal biases in interpretations and choices of source material; affected by availability and weaknesses of primary literature
- Gray literature: material that is not available through traditional systems of publication and distribution
  - Aims vary from dissemination of preliminary scientific data to communicating trade information and opinion
  - Conference proceedings, posters, and abstracts; academic theses, lecture notes, and presentations; industry and government reports and fact sheets; and online blogs, newsletters, advice columns, and community forums

- Difficulties and limitations: rarely undergoes formal peer-review; often contains nonscientific data, unsubstantiated claims, and opinions and experiences from subject matter experts, novices, or even lay people

Primary literature and systematic reviews and meta-analyses are considered to provide the most up-to-date knowledge for dynamic areas of veterinary medicine, such as diagnostic testing and therapy.[4] A systematic review involves a comprehensive search for relevant evidence, followed by critical appraisal conducted according to specific scientific criteria[5]; in contrast, a narrative review or knowledge summary selects and appraises source material according to more subjective and intuitive methods that are at greater risk of bias.[6] Knowledge summaries are intended to be time-saving evidence-based distillations of current research and could become increasingly valuable to EBP veterinarians if the number, scope, and rigor of available summaries improves. Textbooks and narrative review articles are appropriate sources for stable knowledge that does not tend to change, such as anatomy and basic principles, mechanisms, and characteristics of disease.[4] Gray literature is often nonscientific and is usually avoided during EBP, except as a source of anecdote and opinion in situations in which no scientific evidence exists.

A comprehensive literature search requires access to academic citation databases or citation search engines.

- Citation databases selectively catalog citations according to a predefined list of journals, publishers, or subject areas.[7] Veterinary primary and secondary literature is largely indexed in CAB Abstracts and Medline (PubMed) databases.[8] PubMed can be searched for free, whereas CAB requires a subscription.
- Citation search engines such as Google Scholar and Microsoft Academic Search are also free to use and comb the Internet for information that appears to be a citation.[7]

Compared with citation databases, search engines are more likely to return nonscholarly results and gray literature in addition to traditional academic citations.[9] Veterinary online subscription services such as VIN (Veterinary Information Network)[10] also provide access to curated selections of citations, conference proceedings, and self-generated gray literature; because these services provide only selective access to information, they generally should not be relied on for effective EBP. Regardless of which search strategy is used, most full-text articles can be accessed only via subscription or pay-per-use services, although some are available through open-source publishing agreements.

To identify potentially relevant research evidence, enter key words from your PICO question into the search engine or database. A good strategy is to start with the patient population (type of animal and problem) and intervention of interest. It is often necessary to try several iterations of search terms before relevant results are obtained. Some potentially helpful search tips include the following:

- Examine the reference lists of relevant articles or book articles
- Try different ways of searching the species or animal type; birds and reptiles are often identified in article titles using both common names and binomial nomenclature (genus and species) or other zoologic taxa (eg, subspecies or family)
- Include the word “veterinary” in searches of small mammals and exotic species

In the author’s experience, the latter recommendation is helpful to narrow the search focus, given the prevalence of preclinical animal research. Search strategies should initially focus on finding evidence that derives from actual clinical patients, rather than colony-housed animals used to study mechanisms of disease and treatment.

As you examine the search output, flag for a more in-depth examination of any articles that seem relevant. In veterinary medicine, and particularly in exotic animal medicine, it is unfortunately common to find no articles that directly address your specific question. For this reason, it is often necessary to retain articles that are partially relevant, even though you might ultimately discard the research as unhelpful during the appraisal process.

APPRAISING THE EVIDENCE

Being able to understand and critically appraise research studies is at the heart of EBP. Practitioners of EBP commonly triage studies using schemes that rank evidence based on the rigor of the study methods, and how consistent results are across similar studies. **Table 2** presents an overview of the different types of evidence and their relative quality. The highest-quality clinical evidence is typically considered to come from high-level syntheses of multiple studies that address specific scenarios and questions.[11] However, this form of evidence generally does not yet exist in veterinary medicine. Rather, most published evidence in veterinary medicine derives from individual studies, many of which are concentrated in the lower echelons of evidence hierarchies.[3] Although available veterinary evidence often provides a relatively low strength of recommendation relative to what is possible, we can still examine and consider it during our EBP process. To do this, we need to understand the basic goals of clinical research and be able to identify major threats to study validity as they might manifest in common veterinary studies, such as case series and cohort studies.

Clinical Research Basics

If we know what causes a disease or complication, we can develop ways to predict, avoid, or treat it; if we know how a medication or surgery affects different patients or disease processes, we are better equipped to recommend treatment appropriately. The main purpose of clinical research is to explore these causal associations between patient exposures and outcomes.

- Exposures are treatments, tests, environmental factors, patient characteristics, diseases; anything that might be the “cause” in a cause-effect relationship.
- Outcomes are the “effect” part of the relationship, typically the development, improvement, or worsening of diseases, side effects, or events.
- Associations are the estimated relationships between exposures and outcomes.

Obviously, we want to know whether true or real associations exist, but in reality well-intentioned research can sometimes result in false or misleading estimates of association. As practitioners, we can also misuse research by extrapolating results to patients or situations to which they do not really apply. The best evidence has both internal and external validity.

- Internal validity means the associations or other results that the study generates are correct, and are not attributable to some rival explanation. The 3 major threats to internal validity are chance, bias, and confounding.
- External validity means the results are generalizable to real-world populations.
- A study’s vulnerability to threats against internal and external validity determines its place in the EBP evidence hierarchy.

It is important to realize that study design hierarchies are merely broad guidelines; for example, a randomized controlled trial is in theory a high-quality design but a real trial could nevertheless lack internal or external validity and generate low-quality

Table 2
Broad overview of characteristics, quality, and strength of recommendation of various sources of evidence

Evidence Quality and Strength of Recommendation		Evidence type	Characteristic features	In veterinary medicine
Highest	Syntheses of multiple individual studies	Summaries and systems	High-level, continuously updated evidence-based syntheses of specific problems; computerized decision-making support systems	Not currently available
		Synopses of systematic reviews and meta-analyses	Summaries of information found in systematic reviews	Not currently available, likely due to lack of systematic reviews
		Systematic reviews and meta-analyses	Comprehensive summaries of evidence surrounding specific research questions	Uncommon; most individual studies are excluded for failure to meet design and reporting criteria
	Individual studies	Synopses of individual studies	Critical appraisals of 1 or more high-quality studies; usually limited to recent works rather than all knowledge to date; published in specialty journals of evidence-based summaries	Uncommon; knowledge summaries that appraise current research are a version of this; variable quality due to inconsistent appraisal criteria and expertise
		Randomized controlled trials	Prospective cohort study in which subjects are assigned to exposure by the investigators and observed over time for outcomes of interest; high internal validity when rigorously designed and conducted	Somewhat common; variable quality due to deficiencies in design, conduct, and reporting
		Cohort studies	Prospective or retrospective design in which subjects are grouped based on exposure status and observed over time for outcomes of interest	Common; can be mislabeled as case series; single-arm and nonrandomized clinical trials are cohort studies
		Case control studies	Retrospective design in which subjects are grouped based on outcome status and exposure histories are compared to determine risk factors for the outcome	Uncommon; retrospective cohort studies can be mislabeled as case control studies
		Case series	Retrospective design in which subjects with a particular outcome are selected and described	Common
		Clinical case reports	Detailed reports of individual subject experiences; typically new or unusual tests, presentations, diseases, or therapies	Common
Lowest		Preclinical studies, expert opinions	Cadaver, in vitro studies; nontarget species; laboratory animals; induced disease models; biomechanical models; editorials and opinions	Common

Quality and strength of recommendation relate to internal validity, generalizability, and consistency of evidence.

evidence. Until there is a consistently high-quality body of veterinary clinical evidence, we should examine individual studies for internal and external validity, rather than assume these properties exist simply because of the design.

Chance

- The chance effect refers to arriving at false conclusions by random error
- The chance effect diminishes as the sample size gets larger
- Statistical analysis is used to determine the number of animals needed to minimize the chance effect, and to investigate whether specific results could be observed due to chance alone

Most clinical research involves studying a finite number of patients who are drawn from and presumed to represent the underlying population of interest. For example, a researcher interested in rabbit limb amputations would study a sample of representative cases and extrapolate the results to the general population of amputees. However, even if the cases are truly a random sample of all amputees, they might fail to accurately represent the larger population due to chance alone. The chance effect (also called random error or random variation) diminishes as the sample size gets larger. This makes intuitive sense; we would naturally be more worried that a study involving only 3 rabbits could miss important outcomes or focus on idiosyncrasies compared with a study of 300 rabbits. When the study objective is to compare groups of animals, investigators should calculate in advance how many animals they will need to study to reasonably exclude the chance effect; this is known as a sample size or power calculation and can be performed for both prospective and retrospective studies. If a sufficient number of animals is included based on this type of calculation, it provides a measure of protection against arriving at conclusions based on chance alone. Much of the statistical analysis reported in veterinary clinical research articles is used to examine the likelihood that a given result could be observed due to chance alone. A small *P* value or a narrow confidence interval can be reassuring signs that the results are probably not due to random error. However, even when analysis demonstrates a low likelihood that a given result would be observed purely by chance, the finding could still be incorrect due to bias or confounding. Imagine flipping a coin and getting heads 99 on of 100 consecutive flips; the chance of this happening is exceptionally small with a fair coin, but the result could reasonably occur if the coin were unbalanced.

Bias

- Bias is a research conduct error that causes an incorrect estimate of association.
- Bias is typically introduced during selection of study subjects and data collection.
- Bias cannot be corrected with statistics or larger sample size.

Bias refers to systematic error in how the research was performed that results in mistaken estimates of association. Bias is essentially a mistake of the researcher, but it cannot always be avoided. When appraising the literature it can be difficult to know whether results are biased, because documenting it depends on knowing the "true" associations, which are generally unknown and the reason for doing the research in the first place! However, we can assess the *potential* for bias by looking at how a study was designed and conducted. If a study is performed using methods that are known to introduce bias, then it is reasonable to assume the results could be incorrect and we should view them with healthy skepticism. On the other hand, if a study is performed with rigorous attention to minimizing bias, then we can be more confident that the resulting estimates will be correct. As discussed previously, this

is the basic premise of the evidence hierarchies. There are 2 main types of bias to be aware of: selection bias and information (misclassification) bias.

Selection bias

Selection bias occurs when the study sample is drawn from the population in a nonrandom way, such that it does not accurately represent the underlying population. There are many ways to introduce selection bias. Using retrospective medical record review to identify cases for a study is apt to introduce selection bias, because in real life, patients with the same condition are not randomly assigned to receive diagnostic tests and treatments. For example, owners and veterinarians might be less likely to choose and recommend intensive treatments for older, sicker animals, in which case medical records will be biased toward the treatment experiences of animals with better initial prognoses. Prospective studies are also at risk of bias, such as by selectively enrolling certain types of patients or comparing outcomes between groups of animals whose owners chose the treatment plan. Selection bias also can occur due to different follow-up between groups of study subjects. Longer follow-up is often available for animals whose owners choose more involved, intensive, or experimental treatments, whereas animals that are treated conservatively and do not require close veterinarian contact are more likely to be lost to follow-up. Another example of selection bias is nonresponse bias, wherein subjects respond to a survey or enroll in a research study who are systematically different from those who do not respond or enroll.

Information bias

Information bias occurs when information about study exposures and outcomes is incorrect, typically due to how the data are collected. This type of bias is also referred to as misclassification bias, because it often involves incorrect classification of some subjects' treatment or outcome status. Information bias can occur if some animals were not given the full course of treatment or received additional unreported medications that could have affected outcome; if tests or outcomes are incorrectly or inconsistently measured; or if information is selectively recorded for different patients. Selective recording of information is common in the author's experience, particularly in medical records; for example, certain clinical signs could be recorded in detail when attributed to medication but otherwise ignored. In prospective studies, it is typically recommended to blind anyone who is making outcome assessments (such as owners or investigators), because they might interpret or record information differently if they know which study group an animal is in. Recall bias is also a form of information bias and can occur when people are asked to remember whether their pets were exposed to certain environments or medications, or whether certain outcomes occurred. People whose pets experienced memorable outcomes could be more likely to remember previous exposures, particularly if they are aware of a potential causal link to the outcome.

Bias is not diminished with larger sample size, and it cannot be corrected for with statistics. Bias can obscure a real association or create a spurious one, and it can cause overestimation or underestimation of the magnitude of relationships. Because all research is at some risk of bias, and most clinical veterinary studies use designs that are particularly prone, bias should be considered among alternative explanations for most research findings. Ideally, researchers should address the potential for bias in their results, and discuss how bias, if present, might be expected to impact the magnitude or direction of associations. In reality, the potential for bias often does not receive a great deal of attention in article discussion

sections, so the responsibility for considering it largely falls on us as readers and appraisers of the literature.

Confounding

- Confounding refers to a third factor that obscures the true association between an exposure and outcome.
- Confounding is likely to occur when comparing groups of patients that are not balanced with respect to baseline characteristics and prognostic factors.
- Confounding can be mitigated by randomization, matching, and statistical adjustment.

Confounding is present when the observed relationship between an exposure and outcome is actually due wholly or in part to the presence of some extraneous variable. A confounding variable is related to both the exposure and the outcome, but does not lie on the causal pathway between them. For example, imagine a study that observes captive bearded dragons fed 1 of 2 different commercial diets according to owner preference. At the end of 6 months, researchers determine that lizards fed diet X have a much lower incidence of metabolic bone disease, and conclude that diet X is protective against disease. However, it turns out that owners who chose diet X were also much more likely to follow other husbandry practices known to reduce the risk of metabolic bone disease. Confounding is present if the lower rate of metabolic bone disease is partly or completely due to these nondiet husbandry practices; for all we know, the diets could be equivalent. It is easy to see how confounding is problematic, because it can lead us to misunderstand important relationships or make improper changes in practice. Unfortunately, identifying confounding is not always as easy as in this example.

Compared with selection bias, which is an error in how subjects are sampled from the population, confounding is not an error but a real phenomenon that we need to account for. This can be achieved either through study design or statistical analysis. Investigators can control confounding by assigning animals to groups that are balanced with respect to potential confounders, using randomization or matching strategies. Randomization is preferred when possible because it will balance both known and unknown confounders, whereas matching can generally only balance on confounders we are aware of. Alternatively, mathematical modeling can produce adjusted estimates of results that account for confounding; examples of these methods include stratification and Mantel-Haenszel estimation, multivariable regression, and propensity scoring. Most veterinary studies use designs that do not naturally balance potential confounders, such as case series, cohort studies, and nonrandomized trials. Furthermore, in the author's experience, veterinary studies often do not attempt to control for confounding mathematically, or have such small sample sizes that statistical adjustment is not feasible. When evaluating comparative therapeutic studies (eg, studies that compare 2 different treatments or doses, or compare treatment with no treatment), it is helpful to think of confounders as prognostic factors; if the treatment groups are not balanced with respect to known or anticipated prognostic factors, such as age, disease severity, and adjunctive therapies, then confounding could exist and distort the results. Many commonly used statistical tests, such as the Fisher exact test, χ^2 test, *t* test, Wilcoxon rank sum test (Mann-Whitney *U* test), simple regression, and log-rank test, simply compare averages or proportions between groups and cannot adjust for confounding. These methods are not incorrect, nor do they necessarily lead to incorrect results, but, if the groups of animals being compared are not

balanced and one of these methods alone is used to identify important associations, it is reasonable to consider whether confounding could be a factor.

Generalizability

Generalizability refers to whether research results can be applied to real-world patients and circumstances.

External validity of the study pertains to whether its results can be generalized to other populations, settings, and times. Even if a study generates valid research findings, the results are not necessarily true for animals outside the source population. Imagine a study demonstrating that a new medication effectively controls hyperadrenocorticism in a sample of ferrets with treatment-naïve unilateral disease; the results might be correct, but we cannot assume the medication would have the same effect in ferrets that have failed prior treatments or have bilateral disease, or in other species. Generalizability of both population characteristics and the exposures themselves should be considered. Studies might not be highly generalizable if they are based on limited populations selected for convenience (eg, only the animals that were treated at a given practice), or if attempts to limit bias and confounding result in very narrow or unrealistically homogeneous study populations, such as through strict inclusion and exclusion criteria. If the environment, equipment, practitioner skill level, or other conditions in the study are different from your practice, recognize that the results might not apply; an imaging study could be highly accurate when performed under special conditions and interpreted by a radiologist, but the same test could perform poorly in another setting.

Boxes 1 and **2** provide lists of questions that veterinarians might consider when working through the appraisal of individual studies, or comparing evidence across studies.

APPLYING THE FINDINGS TO THE PATIENT

During the appraisal process, we try to understand cause and effect by looking at groups of patients, but ultimately, we need to make recommendations and

Box 1
Practical questions for appraising an individual research study

- How likely is this evidence to be true?
  - Did the study include a large enough number of animals?
  - Is there potential for selection bias in how subjects were chosen for the study?
  - Is there potential for information bias in how data were collected?
  - Does the study account for potential confounding?
- What are the results?
  - What associations (cause-effect relationships) are being investigated?
  - Was an appropriate and balanced comparison made?
  - Were all clinically important outcomes (benefits and harms) considered?
  - Are the conclusions supported by results, considering any limitations?
- Does this evidence generalize to my clinical problem?
  - Does it involve actual clinical patients (vs laboratory animals, cadaver specimens, and so forth)?
  - Are the animals similar to my patients in terms of signalment, disease severity, prognostic factors?
  - Can I provide the test or treatment as described in the study?
  - Are the likely benefits worth the potential harms?

Box 2
Practical questions for synthesizing information from multiple studies

- Is there a systematic review, meta-analysis, or evidence-based knowledge summary related to my question?
- Do the studies include information from a large enough number of animals?
- Are the populations similar across studies and similar to my patient?
- Is the potential for error and confounding similar across studies?
- Are the conclusions generally consistent across studies?

decisions for our specific patient or problem. It is difficult to predict what might happen for any individual animal, but we can use research evidence to understand the spectrum of options and outcomes, reconcile the data with our own experiences and knowledge, and present the possibilities to pet owners. Balancing the different factors (the patient's state, the client's goals, the veterinarian's experience, and the available evidence) typically requires sorting through trade-offs,[2] and even more critically, doing so in a way that is useful to our clients. Determining the role clients wish to play in decision-making and providing the information they need to make an informed choice is a growing responsibility of clinical expertise.[2]

When evidence is identified that is both valid and relevant, clinicians also can use it to implement discussions with team members or to create clinical protocols; EBP can be particularly impactful when the process of appraisal and action is shared and includes the perspectives and experiences of the whole clinical team.[12] Even if the overall evidence is sparse, low quality, or does not truly generalize to your particular patient, the EBP process still helps ensure that new and potentially valuable information has not been missed, and that critical patient care decisions incorporate the best available knowledge.

SUMMARY

High-quality clinical practice requires veterinarians to stay abreast of new research and integrate relevant findings into patient care. Clinicians can achieve this goal using the stepwise EBP method of integrating best research evidence into existing clinical decision-making processes. Practitioners must have access to current citations and full-text publications to fully implement EBP in the information age. Although a high-quality evidence base is lacking in many areas of veterinary medicine, clinicians can use basic clinical epidemiology skills to appraise and integrate available research evidence into clinical practice.

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