

# Forum

## Can Addiction Research Be Trusted?

### Introducing EBAM\* (\*Evidence-Based Addiction Medicine)

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#### Why is Good Research So Important?

Scientific research affects all aspects of medical practice. And, in the addiction treatment field, there is an especially urgent need for *good science* to help overcome stigma, prejudice, and misunderstanding.

Yet, *medical research is an imperfect science*. Understanding principles of clinical research and the nature of those imperfections is essential for becoming *a more critical reader of addiction research literature and a more intelligent consumer of scientific evidence*.

Furthermore, regulatory oversight of addiction treatment programs requires adopting scientifically-validated practices for improving patient care and outcomes. Increasingly, programs also will need to gather and interpret their own research data for reporting results of their efforts as part of the ongoing accreditation process.

Toward those ends, this report introduces some basic principles for evaluating clinical research articles. These will help you determine when research is valid and relevant for your informational needs, and if it might contribute to better patient care.

#### What is the Role of EBAM?

Evidence-based addiction medicine (EBAM) may be defined as *the use of current best evidence in making decisions about the care of individual patients*. It combines clinical expertise with the best available research on a topic of concern gathered from various sources.

EBAM approaches empower addiction treatment providers to clearly differentiate between clinical practices based on sound scientific evidence versus those founded more on traditional practice, outdated beliefs, or “junk science.” Furthermore, in this era of managed care and increasing pressures of accountability, evidence-based practices can help respond convincingly to questions such as:

1. Where did you hear about that treatment?
2. How do you know the information is worthwhile and true?
3. What do you propose doing and what results do you expect?
4. What are the costs versus benefits?

#### Why Be Cautious?

*Medical writing is often biased*. This reflects the fact that there is a specific goal behind any research endeavor to begin with and a particular point of view expressed in the presentation of data. Research articles are a form of persuasive communication, no matter how scientifically objective they appear through the skillful use of language.

Also, it cannot be assumed that everything appearing in print is worthwhile or valid. Authorities in medical publishing have conceded that many wrong, or at least unreliable, answers have appeared in research articles. Numerous investigations of reputable medical journals, spanning many years, have found a surprising number of faults:

- On average, approximately half or more – ranging from 25% to 90% – of all articles in the journals examined contained errors of one type or another, some more serious than others.
- Abstracts accompanying journal articles often receive the greatest attention. Yet, from 18% to 68% of abstracts examined contained data that were inconsistent with or absent from the main body of the articles.
- In one investigation, 80% of randomly selected systematic reviews and meta-analyses were judged to have serious and extensive flaws.

These claims point toward the need for careful and cautious examinations of published medial literature.

## A Closer Look at Research Articles

Many research approaches have been devised over the years, and each has strengths and weaknesses. From a clinical *treatment* perspective, which is the concern here, addiction research seeks to discover improvements in specific aspects of patient care by using certain *interventions*, such as medications or behavioral therapies.

In typical clinical trials, a group of patients exposed to an *Experimental* intervention is compared with patients in a *Control* group receiving a placebo or comparison intervention. Performance on specific *outcome measures* (eg, retention in treatment, illicit-drug abstinence) is used as evidence of effectiveness.

No matter how large the study, each group contains only a relatively tiny sampling of subjects representing a much larger patient population. Statistical analyses use data collected from the sample groups to estimate what the effects might be in that larger population, and whether the performance outcomes of the Experimental versus Control groups significantly demonstrate either beneficial, harmful, or neutral effects of treatment.

## Basic Article Organization

Fortunately, most clinical research reports in medical journals are presented in similar formats. This makes the assessment process easier and more efficient.

The various components are described in **Table 1**. Sometimes, papers depart from the neatly organized presentation outlined in the table. For example, those exact titles may not be used as section headings, or the discussion and conclusion sections might be combined. But, whatever the headings or subheadings, all of the information should be covered in some fashion.

**Table 1: Anatomy Of An Article**

<b>Abstract</b>	Presents a brief overview of the article, including key data from the sections below.
<b>Introduction</b>	States the purpose of the study, including clinical background and rationale, reviews previous studies, and identifies the current questions (hypotheses) to be investigated.
<b>Methods</b>	Defines the patients (subjects) included in the study and sample sizes, describes how the study was conducted (treatment protocol), defines the outcomes measured, and generally describes the statistical analyses to be performed.
<b>Results</b>	Describes in detail what was found during the study, including differences in treatment effects (outcomes), their significance ( <i>p</i> - values) and confidence limits. This section should also show how statistical procedures were performed and specify any adjustments that were made to the data (eg, including or excluding patients lost to follow-up).
<b>Discussion</b>	Interprets the findings and describes any limitations of the study or other factors that might have influenced the results in one way or another: eg, bias in selecting subjects or possible conditions that might have affected outcomes.
<b>Conclusion</b>	Suggests how, when, and in whom the results might be applied in clinical settings and often provides suggestions for further research.

Many persons merely read the article abstract. However, as noted above, this may contain inaccuracies, and the abbreviated presentation of facts can be misleading. If a study appears to be of interest and importance, it is essential that the whole article be examined.

## Levels of Scientific Evidence

Various types of research studies assessing clinical therapeutic effects may be ranked according to a “hierarchy of evidence.” This is based on the relative strength of each study for providing results that are likely to be free of bias and useful to practitioners. Rankings from weakest at the bottom to strongest at the top are shown in **Table 2**.

The ranking does not question the ability of a research approach to be valid and of value for a particular purpose. However, it does recognize that certain forms of evidence may be given greater emphasis for guiding clinical decision-making. Following, from lowest to highest ranking, is a brief description of each type of study.

## Perspectives Articles

“Perspectives” is a coined term to represent *overviews, reports, commentary, editorials, and interviews*. These are the most common types of communications in the addiction field and are often cited as evidence. They are at the bottom of the evidence hierarchy because they summarize or comment on research that was done by others, rather than generating original data from clinical experimentation.

They are subject to bias, such as favoring one viewpoint (perspective) over another. However, these articles can be invaluable sources of information by consolidating existing evidence and offering interpretations to aid understanding and further inquiry by the reader.

## Case Reports

Also called *case histories, case series, or anecdotes*, these draw from personal observations or medical records reviews to report unusual or unexpected events in conjunction with a medication or therapy. There can be biases associated with such reports, including errors in observation, inadequate data, and unsupported conclusions.

Small-scale investigations, enrolling few participants and sometimes called “pilot studies,” might be viewed merely as a case series or collection of anecdotes. And, as Alan Leshner, PhD, former Director of NIDA, frequently stressed, “The plural of anecdote is not evidence.”

## Cross-Sectional Studies

These investigations – also called, *prevalence or epidemiological studies* – examine relationships between medical conditions and other variables of interest as they existed in a defined population *during a particular time*. Researchers look at interventions or exposures (what occurred in the patients) and outcome conditions (what happened). This type of study can establish *associations* but not exact causes of what happened. There may be problems with recall bias (not remembering exactly what occurred), and unknown extraneous factors (confounders) that are unequally distributed among subjects.

## Case-Control Studies

Also called *case-referent, case-comparison, or retrospective studies*, these identify patients with the outcome(s) of interest (Cases) and Control patients without the same outcome(s). The researchers then look back in time to compare how many subjects in each group had the same interventions or exposures of interest. This is a rela-

**Table 2: Hierarchy of Evidence**

<b>Systematic Reviews &amp; Meta-Analyses of RCTs</b>
<b>Randomized Controlled Trials (RCTs)</b>
<b>Cohort Studies</b>
<b>Case-Control Studies</b>
<b>Cross-Sectional Surveys</b>
<b>Case Reports</b>
<b>Perspectives</b>

tively fast and inexpensive method, and it may be the only feasible alternative for examining long-term treatment effects or other outcomes with long lag times between interventions and outcomes. A problem is that this method is highly subject to recall bias or inconsistent records for determining what occurred in the past.

## Cohort Studies

Cohort studies – also called, *observational, followup, incidence, longitudinal, or prospective studies* – are the most common form of clinical trials in addiction medicine. A single group may be involved, but usually two or more groups of patients (cohorts) are enrolled and either receive the treatment of interest (Experimental group) or do not (Controls). The groups are followed forward in time to observe outcomes of interest.

Problems include a lack of random assignment to groups, and difficulty in identifying Control patients similar to those treated or lack of a suitable Control group entirely. Outcome effects also may be influenced by unknown or uncontrolled factors (confounders).

## Randomized Controlled Clinical Trial (RCT)

RCTs are considered by many as the “gold standard” when addressing questions of medication or therapeutic efficacy. In this design, patients are carefully selected and then randomly assigned to Experimental and Control groups, which are followed for the outcomes of interest. The groups are equally matched demographically (eg, age, sex, etc.) and any extraneous factors (confounders) are assumed to be equally distributed across groups.

Unfortunately, this type of study can be the most costly in terms of time and money. Furthermore, in addiction medicine, there may be ethical problems with Control conditions – such as denial of treatment or inadequate treatment resulting in adverse outcomes – and there may be volunteer bias in terms of which patients are willing to be randomly assigned to Experimental or Control procedures for treating their addiction problems.

## Systematic Reviews & Meta-analyses

Systematic reviews gather all available evidence of the highest quality available to address clinical questions. Conclusions tend to be reliable and accurate, depending on the quality of available evidence. Most important, this type of study allows readers to rapidly absorb large amounts of research, and clinical practice guidelines often come from the systematic review process.

Meta-analyses take systematic reviews a step further by combining statistical evidence from multiple investigations and using mathematical techniques to analyze the results. This approach allows for achieving greater precision and clinical applicability of results than is possible with any individual study or systematic review.

## How is Validity Determined?

Questions of validity consider whether reported research results accurately represent the effects of treatment. Basically, can the research be trusted as being correct and free of bias?

There are two general types of validity:

- **Internal validity** is the degree to which research results are likely to be accurate and true for the subjects *in a particular research study*.
- **External validity** – also called generalizability – is the extent to which the results of an investigation might apply to populations beyond those in the particular study, such as in typical addiction treatment settings.

Validity is determined in large part by examining sources of potential *bias* in a study. This has been defined as anything that influences and possibly distorts the results.

The question is not *if* a particular study reflects bias, but *how much*, and whether the biases are sufficient to negate internal and external validity. Bias takes many forms, some more obvious than others.

## Publication Bias

To begin, there are potential biases influencing which studies even appear in print. Investigations with significantly positive results, favoring the Experimental treatment, are more likely to be submitted for publication than those with negative or equivocal outcomes (*publication bias*). This can make it appear that certain treatments are more effective than might be the case.

Also, even in the best of circumstances, it can take years from the time of data gathering until a study appears in print (*time-lag bias*). The latest revelations appearing in today's journals may be completely overruled by studies already waiting in the publication pipeline.

## Patient Selection

When two or more groups of subjects are compared, an important goal is for them to be as similar as possible, *except* for any specific differences under examination. However, even when study-group composition is equivalent, or if only a single group is examined, the chosen subjects may exhibit obvious selection biases that could affect external validity. For example, a study may include only males or younger persons.

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## Subject Management

Other than the intervention under investigation, Experimental and Control groups should have been treated or managed the same; otherwise, the results could be weakened or slanted. This can be difficult in addiction research using behavioral interventions, whereby psychosocial therapies delivered by more than one psychologist or counselor, or at multiple research sites, may not be precisely identical.

## Randomization

The essential principle of randomization is that any research subject has the same and equal chance of assignment to any study condition. In this way, any extraneous factors that might influence outcomes are equally present in all groups, and observed differences between groups are presumably due only to the treatment under investigation. Many research designs in addiction medicine do not use randomization, and the likely existence of associated bias needs to be carefully considered.

## Blinding (Masking)

Patients, clinicians, and other study personnel who are aware of just who is, and who is not, receiving a treatment of interest are likely to form opinions about its efficacy. This may distort other aspects of treatment as well as the reporting of outcomes. Such bias is avoided by double-blinding (also called, “double-masking”), in which neither patients nor study personnel know who is in the Control or Experimental groups.

## Placebo Effects

Bias can occur when a response to drug therapy — regardless of whether it is active medication or an inert placebo — is due to the mere **expectation** of either some *benefit or harm*. This is called the “placebo effect,” and the only way to eliminate it is with double-blind research designs.

## Confounding Factors

Confounders are extraneous factors, such as drugs or physical conditions, that interfere with the research. They may prevent an outcome of interest from occurring or cause it to occur when it otherwise might not. Confounders that are *known and measured* can be controlled using certain statistical manipulations. Randomization is the only way to control for factors that are *not known or not measured*.

## Compliance & Followup

Participant adherence to study protocol (ie, the plan for conducting a study specified in the methodology section of a report) and trial completion are essential ingredients for valid outcomes and conclusions. Yet, these can be difficult to achieve.

Some subjects will disregard instructions and/or drop out during the course of a trial, and the exact reasons are often unknown. This can be especially problematic in addiction research, which often involves an unstable population that is not known for adhering to instructions. However, enrolling only patients with the most potential for full compliance and participation raises questions about selection bias and external validity.

## Completeness of Data

The most thorough approach to overcoming bias in assessing outcomes takes into account all data on *all* patients originally allocated to study groups. That is, all patients who enrolled in a study with the intention of being treated are analyzed as if they received full treatment; even if they dropped out early, did not take all of their medication, or deviated from the protocol in other ways. This is called an *intention-to-treat (ITT) analysis*.

Another strategy is a “per-protocol” analysis of data. For this, researchers take into account *only* those patients who completed all, or a specified proportion, of the study and were compliant with the study protocol to at least a certain degree. Those who dropped out early, or did not take adequate medication or attend sufficient therapy sessions, are excluded from the analysis.

A per-protocol approach can bias results in favor of the Experimental treatment, but it makes sense when the groups are not randomized to begin with or many subjects are lost to followup. It also might be justified in addiction research when outcome success hinges *specifically* on retention in treatment and compliance with taking medication or attending therapy groups.

## Why Good Research Goes Bad

### Problems of Authorship

The role of researcher-author can be difficult. Many challenges must be overcome to initiate a project and see it through to publication, and some of these are listed in **Table 3**.

The research design-to-publication process can take years. Rarely, if ever, is an author allowed sufficient space to *fully* explore the subject at hand in the published article. And, if there are multiple authors, the writing process becomes much more complicated. Some flawed papers are reminiscent of the old saw about a camel being a horse that was designed by a committee.

**Table 3: Challenges Faced by Researcher Authors**

<b>Insufficient Funding</b>	Good research can be costly and researchers may opt to do “something” even when funds are not available to “do it right.”
<b>Inadequate Training</b>	Researchers who are primarily clinicians may not have adequate training in research methodology, analysis, and/or reporting.
<b>Lack of Tech Support</b>	Many researchers do not have access to data processing and statistical support staff.
<b>“Publish or Perish”</b>	Researchers may be under pressure to publish, influencing them to generate more data than necessary and to “dredge” available data for positive results or multiple articles.
<b>Hidden Agendas</b>	There may be “political” influences promoting the exploration of certain hypotheses or demonstrating particular results that are beyond the researcher-author’s control.
<b>Journal Space Limitations</b>	Most journals limit the length of articles, causing authors to carefully choose what is included or deleted. Subtle censorship often fosters inadequate reporting of analyses.
<b>“Too Many Cooks”</b>	Multiple authors and/or peer reviewers complicate the writing process and presentation of results.

### Dangers of “Data Dredging”

Researchers are often tempted to examine their data after the study ends searching for “interesting results” that were not predicted or expected. This is called *“data dredging.”*

For example, outcomes in subgroups of subjects from the overall study population – such as, females or persons of a certain age – may be analyzed looking for significant differences. Such analyses may show that the treatment had a different or better effect in the subgroup.

In some cases, such patients may be more typical of those in a particular clinic setting and the information can be helpful. However, if these analyses were not planned in advance their validity might be questioned; since, if a researcher looks long and hard enough, some sort of significant results are bound to turn up purely by chance.

### Laboratory Versus Clinical Evidence

Research using animals or test tube cultures has greatly contributed to addiction medicine, and can help inspire clinical trials of treatments in humans. However, results of laboratory investigations do not necessarily apply to outcomes in people.

In published articles, there is frequently a biased leap of interpretation from laboratory data to likely effects in humans. This can be misleading, since the ultimate test of a treatment is in patients, “at the bedside” so to speak.

## Distortions in the Mass Media

Finally, medical journalists usually lack an in depth understanding of clinical research methodology and of common biases in such investigations. Meanwhile, news editors seek sensational health stories that will seize the public’s attention.

Journals, research organizations, and researchers themselves often issue press releases on newsworthy investigations. However, these may not sufficiently emphasize study limitations, and data are often presented in formats that exaggerate the perceived importance of the findings.

Consequently, research results are too often misrepresented to the public as scientifically sound evidence when that is not the case. Critical readers need to be watchful for what is essentially *medical propaganda*.

## Putting Research Into Practice

### Everyday Relevance

Clinical research reflects the *potential* for treatments to have certain outcome effects within certain limitations – but not necessarily the “realities” of everyday practice. To be useful in particular addiction treatment settings, research must satisfy essential questions of relevance:

- Overall, does the study represent high quality, valid evidence?
- Do the questions (hypotheses) addressed by the study pertain to your needs?
- Are the study subjects similar to your own patients?
- Is the research methodology free of bias and clearly explained?
- Are the results understandable and statistically significant?
- Do the conclusions make sense from patient-benefit perspectives (clinically significant)?

Above all, clinical research outcomes should satisfy the last question by helping to define best practices, with important benefits for patients outweighing any disadvantages.

## Developing a Healthy Skepticism

In response to the title question of this report: Yes, addiction research can usually be trusted. However, you need to learn what to look for in assessing the quality of research.

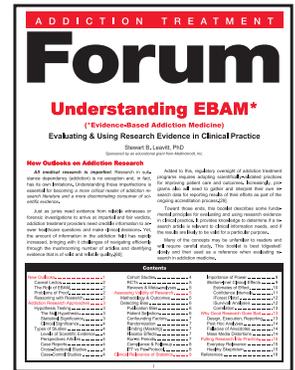
At the very least, addiction treatment providers need to develop a healthy skepticism and become more critical in

their reading and acceptance of research literature. Being aware of the potential for biases, flawed study designs or analyses, and inappropriate reporting methods can help in avoiding untrustworthy data.

You also can help promote better addiction research by supporting and subscribing to only those publications offering the highest quality articles presenting valid research evidence. Similarly, research-funding organizations and agencies should be pressured to adopt higher standards of quality in all phases of addiction research, from design to publication. Finally, biased or slanted research reporting in the mass media or other information sources can be challenged by writing letters of complaint.

### For further information see...

“EBAM for Practitioners” provides a more in depth and technical look at evidence-based addiction medicine principles and assessment tools. This 16-page booklet is available for download in PDF format at <http://www.atforum.com> (under the Addiction Resources tab).



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