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How to read clinical journals: V: To distinguish useful from useless or even harmful therapy

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This consecutive series of Clinical Epidemiology Rounds is presenting efficient and effective strategies for busy clinicians to use when reading clinical articles. The general rules for reading clinical articles are summarized in Fig. 1. This final round will consider the reading of clinical journals to distinguish useful from useless or even harmful therapy; the guides for doing so are listed in Table 1. The necessity for this distinction is underscored in the following clinical presentations.

A. A 48-year-old executive is found to have an elevated serum cholesterol level at his annual company-sponsored check-up. He has a negative history and a normal physical exam, and his resting electrocardiogram is not remarkable. A low-fat diet and clofibrate are prescribed.

B. The son of a man who underwent gastric freezing for a duodenal ulcer 15 years earlier is also found to have a duodenal ulcer and is given cimetidine.

C. A circumferential ligature is placed in the cervix of a pregnant woman with a history of spontaneous abortion.

D. A man with severe angina pectoris and severe left main-stem coronary artery narrowing undergoes aortocoronary bypass grafting on a surgical service that previously carried out internal mammary ligations.

E. After 6 months of inpatient therapy for schizophrenia, a woman is discharged with a prescription for imipramine.

F. A child in whom tuberculous meningitis is diagnosed is immediately given streptomycin (plus isoniazid and rifampin).

G. Two elderly men with transient ischemic attacks are admitted to hospital. One undergoes carotid endarterectomy and the other is begun on a long-term regimen of acetylsalicylic acid.

H. Following a blood pressure rise from 110/70 to 140/90 mm Hg, a pregnant woman is given methyldopa.

I. A woman has polyarthritis and a positive test for rheumatoid factor. Indomethacin is prescribed.

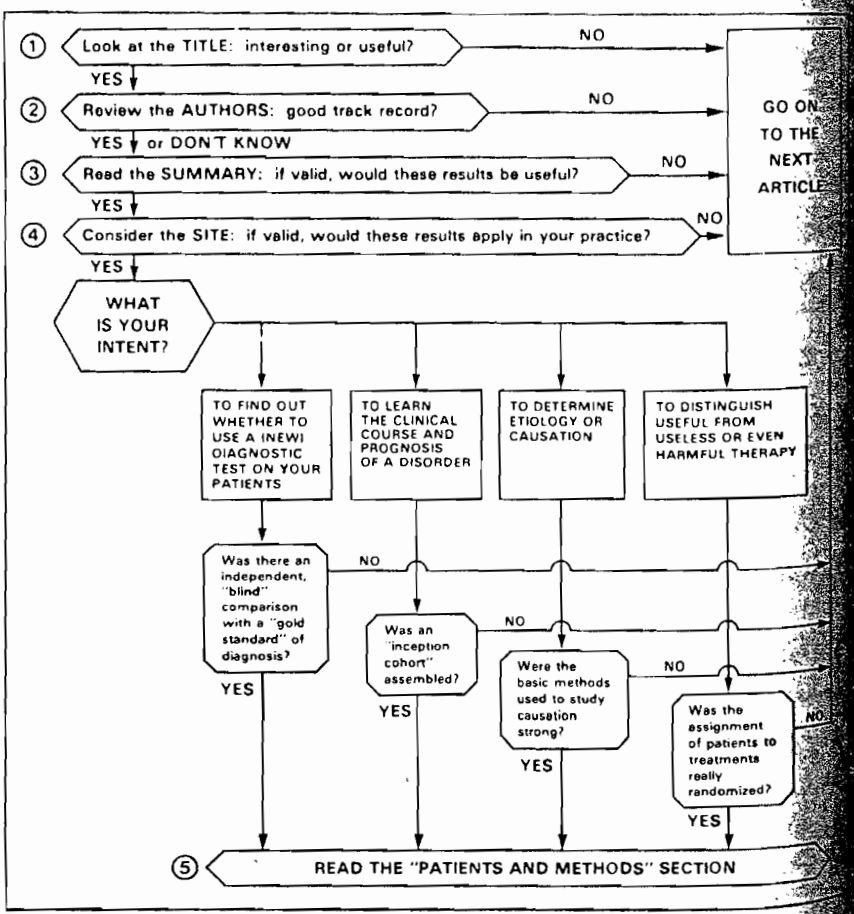

FIG. 1—The first steps in how to read articles in a clinical journal.

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J. A child whose 35-dB hearing loss was detected on a preschool exam is booked for tympanostomy and tubal insertion.

These patients have several common features: the central one for this round is that all of them were given treatment intended to prevent (clofibrate in case A), cure (streptomycin in case F) or ameliorate (indomethacin in case I) the disease or illness. Furthermore, all of these interventions were based on the results of basic research into human biology* and behaviour, and case series have clearly documented excellent clinical outcomes among patients receiving each of these interventions.

None the less, although we accept some of these treatments as clearly efficacious (that is, we are convinced that they do more good than harm to patients who comply with them), we are doubtful about others and mock the consensus of a former era that embraced gastric freezing and internal mammary ligation. Why is this? One major reason is that we are willing to learn from experience; the treatments that do more harm than good are, we hope, eventually unmasked. More important, however, is the growth of the attitude, at least in this country, that claims for efficacy need to be backed up by solid evidence, typically from randomized clinical trials, before clinicians will accept them.

This final round will show how to apply some common-sense rules of evidence to the claims for efficacy that appear in clinical journals.

Readers' guides

The rules of scientific evidence for the study of therapy can be summarized into six guides for the busy clinical reader (Table I). Once again, they constitute "applied common sense" and are designed to maximize the efficiency as well as the accuracy of your clinical reading. These guides are of two sorts, as shown in Table I; the first and last deal with *validity* (Are the results of the study likely to be *true?)* and the second, third and fifth guides deal mostly with *applicability* (Are the results of the study likely to be *useful*?). The fourth guide deals equally with elements of both validity and applicability.

1. *Was the assignment of patients to treatments really randomized?*

Every patient who entered the study should have had the same *known* probability (typically 50%) of receiving one or the other of the treatments being compared; thus, assignment to one treatment or another should have been carried out by a system analogous to flipping a coin. It's usually easy to decide whether this was done, for key terms such as "randomized trial" or "random allocation" should appear in the abstract, the Methods section or even the title of such articles.†

As a result, the busy clinical reader has the option of applying this guide rigorously: if you are reading a journal to which you subscribe to "keep up with the clinical literature", rather than searching the clinical literature to decide how to treat a specific patient, discard at once all articles on therapy that are not about randomized trials.

Why such a strict criterion? Why shouldn't clinicians accept the results of trials that are not randomized? A formal explanation for this strict rule is lengthy, but its conclusion is straightforward: random allocation eliminates many of the biases that lead to false results in nonrandomized trials. The pragmatic explanation is brief: we are very much more likely to help our patients and very much less likely to harm them if we institute therapies that have been shown to do more good than harm in proper randomized clinical trials.

Instances in which we have been misled by accepting evidence from nonrandomized trials are numerous and include several of the case presentations that opened this round. For example, clofibrate, as used in case A, was growing in popularity before publication of the randomized clinical trial that showed that it actually increased mortality;[2] the drug was subsequently banned in several countries. Furthermore, it has been estimated that 2500 gastric freezing machines had been used in treating tens of thousands of patients with peptic ulcer — for

*Yes, even internal mammary ligation, for contemporary research had shown that substances injected into the stump of the internal mammary artery could be recovered shortly thereafter from the coronary circulation.[1]

Table I—A detailed view of readers' guides for intervention studies

Validity (Are the results likely to be true?	1. Was the assignment of patients to treatments really randomized?	
	2. Were all clinically relevant outcomes reported?	
	3. Were the study patients recognizably similar to your own?	Applicability (Are the results likely to be useful?)
	4. Were both statistical and clinical significance considered?	
	5. Is the therapeutic maneuver feasible in your practice?	
	6. Were all patients who entered the study accounted for at its conclusion?	

†Beware of "look-alikes" to randomization. For example, some reports describe how patients were assigned "at random" to one therapy or another; often these are *not* randomized trials; the authors of such reports might as well have said that patients were assigned "at the investigators' convenience", "without conscious bias" or even "haphazardly".

example, the father in case B — before a randomized trial demonstrated the lack of efficacy of this treatment.[3] Finally, it took a randomized clinical trial in which patients with angina were randomly allocated to undergo or not undergo internal mammary ligation only after their arteries had been surgically exposed to impress on us how often symptomatic improvement can follow placebo medications and procedures.[4]

In summarizing the situation as it applied to the treatment of rheumatic fever, Bywaters[5] suggested that the proponents of different regimens may be grouped as those with enthusiasm and no controls and those with controls but no enthusiasm. This state of affairs was actually quantified for therapeutic maneuvers in pediatrics by Sinclair,[6] who classified articles on the treatment of respiratory distress syndrome by whether there were controls and whether the authors concluded that therapy was efficacious; his results appear in Table II.

In summary, then, although the randomized trial can sometimes produce an incorrect conclusion about efficacy (especially, as we shall find out shortly, when it is a small trial), it is by far the best tool currently available for identifying the clinical maneuvers that do more good than harm.

Can we *ever* be confident that a treatment is efficacious in the absence of a randomized trial? Only when traditional therapy is invariably followed by death. Consider case F: Prior to 1946 the outcome of tuberculous meningitis was invariably death. Then, when small amounts of streptomycin became available for use in the United States a few victims treated with this new drug survived.[7] This remarkable result was repeated shortly thereafter in the United Kingdom.[8] Thus, the ability to show, with replication, that patients with a previously universally fatal disease can survive following a new treatment constitutes sufficient evidence, all by itself, for efficacy.

By insisting on evidence from randomized clinical trials you can increase the efficiency with which you read a journal to which you subscribe, for it will lead to early rejection of most of the articles concerned with therapy. The rule requires some modification, however, for reading about a particular patient; often in this instance no proper randomized control trials have ever been published. What should the clinical reader do then?

Two sorts of actions are appropriate when reading about a specific patient. First, the initial literature search should be for any randomized trials that do exist. Second, in the absence of any published randomized clinical trials, clinical readers will have to use the results of subexperimental investigations. Before accepting the conclusions of such studies, clinicians should be satisfied that the improved patient outcomes following therapy are so great that they cannot be explained by one or more biases in the assembly of the study patients or in the assessment or interpretation of their responses to therapy. This second rule is obviously a judgement call and should be tempered by the recollection that this same sort of subexperimental evidence supported the earlier use of clofibrate, internal mammary ligation and gastric freezing. Thus, the situation is a familiar one for clinicians: the need to act in the face of incomplete information. As in similar circumstances this is perhaps best accomplished by considering both the certainty of causation and the consequences of the alternative courses of action (see part IV of this series): Does the patient require *any* intervention? If so, have any of the available interventions been shown to do more good than harm in a randomized trial? If not, which of them is most likely to produce a favourable trade-off between benefit and risk? The following guides may be useful in the critical assessment of proper randomized trials.

2. *Were all clinically relevant outcomes reported?*

Consider Table III, which summarizes the results of an important randomized trial of clofibrate among men with elevated levels of serum cholesterol.[2] Some of the outcomes of therapy appear highly favourable. For example, the serum cholesterol level — a key risk factor for coronary heart disease — fell by almost 10%, providing some biologic evidence for benefit. However, some readers will recognize a claim of therapeutic benefit based on this change in the serum cholesterol level as an example of the "substitution game", in which a risk factor is substituted for its associated clinical outcome,[9] and will want to look further to see whether there were real changes in the occurrence of acute coronary events.

Such evidence is also available in Table III, where we note reductions in the numbers of nonfatal myocardial infarctions and of all infarctions, both fatal and nonfatal. Thus, the efficacy of clofibrate appears to be supported in this study. However, when we consider all the clinically relevant outcomes, especially from the patient's point of view,[10] we must consider the effects of clofibrate on the quality of life and on total mortality; this is shown with disturbing clarity in line 4 of

Table II—Relation between alleged therapeutic benefit and the use of control groups*

Type of study	No. of studies (and % reporting therapeutic success)
Without controls	19 (89)
With controls	18 (50)

Fisher's exact probability = 0.01.

*Adapted from reference 6.

Table III—Clinically relevant outcomes in a randomized trial of clofibrate for preventing coronary heart disease*

Variable	Outcome: With placebo	Outcome: With clofibrate
Average change (%) in serum cholesterol level	+1	−9
No. of nonfatal myocardial infarctions/1000 men	7.2	5.8
No. of fatal and nonfatal myocardial infarctions/1000 men	8.9	7.4
No. of deaths/1000 men	5.2	6.2

*Adapted from reference 2.

Table III: the death rate rose with clofibrate therapy, a result that subsequently has profoundly affected both the use and availability of this drug. Thus, because one's judgement about the usefulness of clofibrate or of other agents can depend, in a crucial way, on the clinical outcomes chosen for comparison, readers must be sure that all clinically relevant outcomes are reported.

Furthermore, because clinical disagreement is ubiquitous in medicine,[11] readers should also recognize the necessity for explicit and objective criteria for the clinical outcomes of interest and for the application of these criteria by observers who are "blind" to whether the patient was in the active treatment or control group.

3. *Were the study patients recognizably similar to your own?*

This guide has two elements. First, the study patients must be recognizable; that is, their clinical and sociodemographic status must be described in sufficient detail for you to be able to recognize the similarity between them and your own patients. Second, the study patients must be *similar* to those in your practice. To put it another way, you should ask yourself: Are the patients in this study *so different* from my patients that I could *not* apply the study results in my practice? This requirement goes beyond the fourth general guide for reading clinical journals (the site) to encompass the precise features of individual patients rather than the general features of their referral network. When both recognizability and similarity are satisfied, clinical readers will be able to predict with confidence the clinical outcomes to be expected from applying specific therapy to specific patients in their practices.

4. *Were both statistical and clinical significance considered?*

Clinical significance here refers to the *importance* of a difference in clinical outcomes between treated and control patients, and is usually described in terms of the *magnitude* of a result. Thus, in Table III we see that the patients taking clofibrate were (6.2 − 5.2)/5.2 or 19% more likely to die than those randomly assigned to receive a placebo. Such a difference becomes clinically significant when it leads to changes in clinical behaviour;* thus, this 19% difference in total mortality is confirmed as being clinically significant when its recognition is followed by a sharp reduction in the frequency of prescribing clofibrate for such patients.

By contrast, *statistical* significance merely tells us whether a difference is likely to be *real*, not whether it is important or large. More precisely, the statistical significance of a difference is nothing more than a statement of the likelihood that this difference is due to chance alone. Thus, if the likelihood is quite low (say, less than 5% or < 0.05†) that the 19% difference in total mortality between patients taking clofibrate and those taking placebo is due to mere chance, we refer to the difference as being statistically significant.

The determinants of clinical significance are therefore the determinants of changes in clinical action; if the results of a study lead you to abandon an old treatment for a new one, the difference in the effects of these treatments is clinically significant. The determinants of statistical significance are not as immediately obvious. Simply stated, the statistical significance of any given result rises (that is, the P value falls) when the number of patients in the study is increased, when the clinical effect of treatment shows less fluctuation from day to day or from patient to patient, and when the measurement of this clinical effect is both accurate and reproducible.

On the basis of the foregoing, the busy reader can use two quick yardsticks for reading therapeutic articles. First, if the difference is statistically significant ($P < 0.05$), is the difference clinically significant as well? If so, the results are both real and worthy of implementing in clinical practice. Second, if the difference is not statistically significant, are there enough patients to show a clinically significant difference if it should occur? As already discussed, the number of patients in a study is one of the determinants of statistical significance. Thus, if a study population is huge, the difference in clinical outcomes can be statistically significant (real) even if it is clinically trivial (too small to justify a change in clinical behaviour). Conversely, if a study population is too small, even large differences of enormous potential clinical significance may not be statistically significant.‡ Readers must therefore scrutinize the difference in clinical outcomes in studies whose results are not statistically significant to see whether they are of potential clinical significance. This admonition has received additional weight from the demonstration that most of the recently published randomized trials whose results were not statistically significant had too few patients to show risk reductions of 25% or even 50%.[12]

5. *Is the therapeutic maneuver feasible in your practice?*

There are four requirements here. First, the therapeutic maneuver has to be described in sufficient detail for readers to replicate it with precision. Who did what to whom, with what formulation and dose, administered under what circumstances, with what dose adjustments and titrations, with what searches for and responses to side effects and toxicity, for how long and with what clinical criteria for deciding that therapy should be increased, tapered or terminated? Second, the therapeutic maneuver must be clinically

*Although we have defined clinical significance from the clinician's perspective, it could, of course, also be defined from the patient's perspective in terms of "important differences in the quality of life".

†By convention this likelihood is called the "P value", "alpha" or "the chance of making a type I error", in which we conclude that a difference exists when, in fact, it doesn't.

‡This is what is meant by "low power", the "β-error problem" or the "risk of a type II error", in which we conclude that no difference exists when, in fact, it does.

and biologically sensible. For example, the dose, route of administration and duration of drug therapy should be consistent with existing knowledge about pharmacokinetics and pharmacodynamics. Similarly, combinations of different treatment modalities should make clinical sense.

Third, the therapeutic maneuver has to be available. Readers must be capable of administering it properly and their patients must find it accessible, acceptable and affordable.

Fourth, when reading the description of the maneuver in the published report, readers should note whether the authors avoided two specific biases in its application: *contamination*, in which control patients accidentally receive the experimental treatment, which results in a spurious reduction in the difference in clinical outcomes between the experimental and control groups; and *co-intervention*, when additional diagnostic or therapeutic acts are performed on experimental but not control patients, which results in a spurious increase in the difference in clinical outcomes observed between the experimental and control groups. Once again, it should be apparent that co-intervention is prevented by "blinding" both study patients and their clinicians as to who is receiving what treatment.[13]

6. *Were all patients who entered the study accounted for at its conclusion?*

The canny reader will note how many patients entered the study (usually the numbers of experimental and control patients will be almost identical) and will tally them again at its conclusion to make certain that they correspond. For example, Table IV describes the clinical outcome in 151 patients in a randomized trial of surgical versus medical therapy for bilateral carotid stenosis.[14] Among 79 patients undergoing surgical therapy and 72 patients undergoing medical therapy who were "available for follow-up" (total at the end of the study, 151) a 27% ($P = 0.02$) reduction in the risk of continued transient ischemic attacks, stroke or death was reported following surgery, a difference that is both clinically and statistically significant. However, closer reading of the report reveals that 167, not 151, patients entered this study and that 16 of them suffered a stroke or died during their initial hospitalization and were excluded from the foregoing analysis. Furthermore, 15 of the 16 patients had been allocated to surgery; 5 of them died and 10 had a stroke during or shortly after surgery. The results of their reintroduction into the final analysis are shown in Table V; the reduction in risk from surgery is now only 16% and no longer statistically significant ($P = 0.09$).

The authors of the foregoing report were careful to include outcome information on all patients who entered their trial, making the construction and interpretation of Table V possible. What can the reader do when the outcomes for missing subjects are not reported? One approach (admittedly conservative and therefore liable to lead to the "type II" error) is to arbitrarily assign a bad outcome to all missing members of the group with the most favourable outcomes. If this maneuver fails to shift the statistical or clinical significance of the results across a decision point, the reader can accept the study's conclusions.

Use of these guides to reading

The approach to the clinical journal described in this and the other Clinical Epidemiology Rounds in this series is designed for busy clinicians who are striving to keep abreast of important advances in clinical diagnosis, of new insights into the clinical course and prognosis of human illness, of breakthroughs in our understanding of the etiology of disease, and of clinically significant improvements in therapeutics. We clinicians face an awesome task: although already behind in our clinical reading, we are asked to absorb the contents of ever more journals each year.

Assuming we will never have more time to read than we do now, and recognizing that critical assessment of the clinical literature is required if we are to do more good

Table IV—Surgical versus medical therapy in bilateral carotid stenosis: outcomes among patients "available for follow-up"*

Therapy	Recurrent transient ischemic attacks, stroke or death: Yes	No	Total no. of patients
Surgical†	43	36	79
Medical	53	19	72

*Adapted from reference 14.
†Risk reduction from surgical treatment: [(53/72) − (43/79)]/(53/72) = 27%. $\chi^2 = 5.98$ and $P = 0.02$.

Table V—Surgical versus medical therapy in bilateral carotid stenosis: outcomes among all patients randomized*

Therapy	Recurrent transient ischemic attacks, stroke or death: Yes	No	Total no. of patients
Surgical†	58	36	94
Medical	54	19	73

*Adapted from reference 14.
†Risk reduction from surgical treatment: [(54/73) − (58/94)]/(54/73) = 16%. $\chi^2 = 2.80$ and $P = 0.09$.

than harm to our patients, we have assembled and described a set of common-sense guides for assessing clinical articles. One of the major results of their application is the early rejection of many, indeed most, clinical articles. No doubt in the process of their application some meritorious publications will be cast aside. None the less, we believe that the subset of clinical articles that survive the application of these guides will be the most valid, the most relevant and the most applicable to our clinical practices; thus, they will merit the increased attention that we, in our less encumbered reading, can pay them.

Conclusion

What proportion of papers will satisfy the requirements for both scientific proof and clinical applicability described in the last five Clinical Epidemiology Rounds? Not very many, although there is evidence that matters are improving.* After all, there are only a handful of ways to do a study properly but a thousand ways to do it wrong. Moreover, even if a study does satisfy all of these requirements it will not settle a clinical question for all time. At best, it will contribute a small, sometimes only temporary, increment to our ability to relieve suffering and promote health. As well, the results and conclusions of even the soundest studies may provoke sharp and continuing controversy.

The reasons for this slow progress and these disputes are several. First is the possibility that, despite impeccable design and analysis, the study results are flat wrong; this, of course, is the inevitable, although rare, consequence of testing for statistical significance: occasionally results *will* be due to chance alone.

Second, the contemporaneous understanding of human structure and function and mechanisms of disease that led clinical investigators to group certain sorts of patients or responses together may subsequently be shown to have been seriously deficient, negating the results or interpretations of the original study.

Third, a study may be misunderstood or misinterpreted by those who read about it, such as when an explanatory trial designed to answer the question "Can treatment X work under optimal circumstances (e.g., compliant patients, elaborate dose-setting schemes and a restricted set of clinical outcomes)?" is criticized for its inability to answer the management question "Does treatment X do more good than harm under usual clinical circumstances (e.g., all patients, usual dose-setting procedures and the gamut of clinical outcomes)?"[10]

Fourth, controversy can arise over the interpretation of even a valid study when a trade-off must be made between the different results it produces. For example, studies of alternative approaches to managing patients with symptoms of appendicitis have shown that one could minimize the number of deaths from this condition with a liberal policy of operation on all such patients, even those with mild symptoms.[16] On the other hand, if one wanted to minimize the amount of unnecessary surgery, hospital costs or length of convalescence one would adopt a more conservative policy and reserve surgery for patients with severe symptoms. In this instance there are not one but two sharply contrasting "best answers" to the clinical question being posed, and controversy becomes inevitable.

Fifth, study results and interpretations, even those that satisfy the requirements set down in these last five rounds, may meet considerable resistance when they discredit the only clinical approach currently available for managing a condition; clinicians still may elect to do something, even if it is of no demonstrable benefit, rather than nothing. Finally, study results may be rejected, regardless of their merit, if they threaten the prestige or livelihood of their audience.

In summary, this series of rounds is intended to help the serious reader afford time for the proper evaluation of that subset of the clinical literature most likely to yield valid and useful new knowledge. Although it would be naive for us to expect the application of these guides to greatly accelerate the acquisition and clinical application of useful new knowledge, we are confident that their adoption will ensure that whatever momentum is achieved will be forward.

Although the readers' guides have been presented for use in reading the current clinical literature, they have other uses as well. For example, they can aid a literature review, focusing our search and assisting in the identification of the most potentially useful articles. Moreover, in clinical discussions at the bedside or in teaching rounds they can be applied to statements about diagnosis, prognosis, etiology and therapy. Finally, they can be used to organize and present evidence about diagnosis, prognosis, etiology and therapy to students and colleagues.

We welcome feedback about the usefulness of this series for all of these purposes as well as suggestions for their improvement.

We thank our students, house staff and clinical colleagues for their suggestions and criticisms of earlier versions of these ideas.

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