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Now You Be the Judge

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In a previous article *(1)* I presented reasons why you should say yes when asked to serve as a peer reviewer. I hope I was able to convince you of the benefits of serving as a peer reviewer and you have accepted an invitation to evaluate a manuscript. Now what do you do? Since you might be blaming me for getting you into this situation, it is the least I can do to provide you with resources and advice on how to review the submitted manuscript. So, in this article I will focus on questions to be answered and information to be gathered as you read the manuscript. In the next article in this series, I will discuss how to write the actual review. I want to emphasize that although I present here what I believe is a good approach, I encourage you to look at the advice of others *(2–9)*, not only because these articles will complement the information that I present but also because you will find important commonalities on how to perform a fair and thorough review of a manuscript.

First Know the Rules

The first step in the process is to learn what the journal wants. Many journals have general or specific guidelines for reviewers that inform peer reviewers of the criteria the journal uses in making decisions regarding publication, factors to be considered when reviewing a manuscript for that journal, the journal's conflict-of-interest policy, and even questions the reviewer should answer when writing the final review. These guidelines are often published as online documents available on the journal's website, so even if you have not received specific instructions from the journal, take a few minutes to educate yourself about the requesting journal's policies and how they want the review to be written. Remember, as a peer reviewer you are not just representing yourself; you are representing the journal and its reputation.

Familiarize Yourself with the Paper

Once you are cognizant of the journal's guidelines and policies for peer review, I recommend doing a first read of the entire manuscript, including any supplemental materials, as soon as possible after accepting the review assignment. At this point, concern yourself only with the content of the paper *(2)*, rather than specific details. Make a preliminary note if something catches your attention, but avoid any prejudgment, because the item may be addressed later in the paper.

Performing an initial read of the manuscript allows you to see whether the manuscript is in such bad shape that a proper review cannot be performed. Journals often tell peer reviewers that they need not concern themselves with spelling or grammar. Sometimes, however, the submitted manuscript is just not sufficiently readable to allow any review, and you should not feel obligated to spend a lot of time trying to figure out what the authors intended to communicate. You can then return the manuscript to the editor in a timely fashion so that the editor can either reject the manuscript or return it to the authors for improvement in language, grammar, or format. Another reason to do a preliminary read of the manuscript is that it allows you to determine early on whether you have any conflicts of interest that should be shared with the editor before you review the manuscript. Once you have had a manuscript for a week and the deadline for returning the review is approaching, you might feel obligated to try to salvage some sort of peer review for the manuscript and possibly misjudge the value of a study rather than admit that you cannot do a fair review of the manuscript. If I were the author, I would want to know as soon as possible that my manuscript did not meet the journal's standards and that improvements in the manuscript were necessary for a proper peer review.

The Hard Look

Now reread the manuscript again. As you do so, consider the questions listed in Table 1. Make specific notes about pluses and minuses you find during this in-depth evaluation so you can go back and compile these notes to create a detailed assessment of the importance of the authors' work, the solidity of the science, the strengths and weaknesses of the study, and what changes (e.g., additional experiments, different statistical analyses, reinterpretation of the data, alternative wording) might strengthen the manuscript. Mark your notes (e.g., "ed" or "au") to help you remember which items should be addressed to the editor

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Table 1. Questions to consider when reviewing a manuscript.

Title
Is the title concise?
Is the title informative?
Does the title accurately reflect the study?
Abstract
Does the abstract follow the required format?
Is there a description of what was studied and why?
Is the question, hypothesis, or goal stated?
Do the authors indicate how the study was performed?
Does the abstract include the important results?
Does the abstract include the answer to the question posed?
Does the abstract include the authors' conclusions?
Does the abstract stand on its own in telling the story?
Does the abstract contain information absent in the main text?
Are all numbers in the abstract identical to those in the main text?
Are there any unclear or undefined abbreviations?
Introduction
Does the background information adequately describe the topic?
Is the subject matter relevant to the journal?
Is a specific problem or knowledge gap identified?
Is it clear why there is a need for the study being reported?
Is the question, hypothesis, or goal of the study clearly defined?
Is the question, hypothesis, or goal novel and scientifically important?
Have others carried out similar studies?
Methods/Experimental
Is the study design adequately described?
Is the study design both valid and rigorous?
Have the authors used appropriate methods?
Are the methods adequately described?
Is there adequate description of reagent preparation?
For commercial kits, is the assay performance described?
Were proper validation experiments performed?
Were samples properly collected, processed, and stored?
Is it clear why each experiment was performed?
Has Institutional Review Board approval been obtained?
Have diagnoses been made by use of valid criteria?
Are the end points of the study clearly defined?
Are sample sizes or patient numbers sufficiently large?
Are there adequate data review and statistical analyses?

Continued in next column

Table 1. Questions to consider when reviewing a manuscript. *(Continued from previous column)*

Results
Are the results presented in a logical manner?
Is the presentation of the results balanced and unbiased?
Is there a result presented for every experiment?
Do the authors provide adequate data to support the results?
Do the results appear to provide an answer?
What is the quality of the data?
Are the figures and tables clear?
Do the numbers add up in tables, graphs, or other displays?
Are all of the figures and tables necessary?
Discussion
Does the Discussion include the answer to the original question?
Do the authors show what the results mean?
Is the authors' interpretation supported by the data?
Is it clear what contribution the paper makes to the field of study?
Are potential limitations of the study addressed?
Has a negative finding been ignored?
Do the authors address any surprising findings?
Is the Discussion balanced?
What are the main conclusions?
Are the conclusions valid and supported by the data?
Is there excessive overlap with the Introduction or Results sections?
References
Do the references show a proper knowledge of the literature?
Is there a balanced selection of references?
Are all references accounted for in the manuscript?
Do the authors try to cite unpublished material?
Do the authors cite manuscripts in preparation or in press?

and which should be addressed to the authors. Each section of a manuscript has a purpose or goal, and you should pay special attention not only to the information presented in each section but also how the sections of the manuscript come together to tell the story. And that story starts with the title.

TITLE

The title draws from the other sections of the paper and becomes the face of the paper *(10)*. There should be only one meaning to the title. It should accurately describe the study. Furthermore, the title should be concise, clear, informative, and relevant to the audience of that particular journal. If you cannot readily understand the title, will others? Lastly, be suspicious of sub-

jective terms such as "novel," "new," or "supersensitive" in the title.

Look at the title that accompanies the abstract in Example 1. There is only one meaning to the title. The topic (ethylene glycol toxicity), the protocol (intravenous narezode added to dialysis), a summary of the results (narezode reduces toxicity), and the population studied (humans) are all mentioned in the title. I would consider this title to be concise yet more informative than a generic title, such as "Narezode Treatment after Ethylene Glycol Ingestion."

ABSTRACT

First determine whether the journal asking for the peer review publishes simple or structured abstracts *(11)*. Make sure that the authors have followed the required format. Regardless of the format, the abstract should contain enough information that it can stand on its own. Regardless of the word limit set by the journal, the abstract should, at the minimum, provide you with a reasonable idea of what was studied (topic), why the authors performed the study (question asked, hypothesis, end goal), what was found during the study (results, answer), and what the results mean (conclusions). Whenever possible within the allowed word count, the authors should also describe the methods used or the experiments performed (how).

The abstract will be the first thing that you, the peer reviewer, will use to make a judgment about the manuscript. Makes notes about the importance of the question addressed in the study, whether the authors actually answered the question or reached their goal, the importance of the answer, and the soundness of the authors' conclusions. As you read the remainder of the manuscript, refer back to the abstract to be sure that the Introduction, Methods, Results, and Discussion sections are consistent with the original question/hypothesis/goal presented in the abstract.

Let's look again at Example 1, which shows the abstract for a study of a competitive inhibitor of alcohol dehydrogenase, the enzyme that catalyzes the initial steps in the metabolism of ethylene glycol. Both the agent, narezode, and the study described are hypothetical. The abstract indicates what was studied (ethylene glycol toxicity), the important knowledge gap (whether narezode works in humans), what was found (narezode reduced metabolic acidosis and renal tubule damage with no side effects), and what conclusions could be drawn from the results (narezode is effective and safe for emergency use). Note that this abstract states that urinary oxalate, blood pH, and urine protein (α_1-microglobulin) excretion were monitored, as well as allergic reactions. Numerical summary data are also included. Thus, as you read the main text, you will want to verify that there are matching methods, results, and numbers for everything described in the abstract.

INTRODUCTION

The goals of the Introduction section are to educate the reader about the topic of the study, to tell the reader why there is a need for the study being reported, to explain the goal of the study, and to stimulate the reader to want to read further. The background material should start with enough information to help you grasp the general field of study and then should transition to the specific aspect of the field the authors studied and an explanation of why it is important. The Introduction should include a description of needed but unknown information, an unsolved problem, a knowledge gap, or limitations of prior studies. Most important, the authors must clearly state the question being asked, the hypothesis being tested, or the purpose of their study. After reading the Introduction, note whether (*a*) the subject matter appears relevant to the selected journal, (*b*) the authors have convinced you that the topic is worth studying, (*c*) a specific problem or knowledge gap is clearly defined, and (*d*) the specific question being asked, hypothesis being tested, or purpose for doing the study is novel and scientifically important. A topic might be interesting and not well understood, yet the rationale presented for studying it is weak. There may be an important problem to be solved, yet the hypothesis, question, or purpose is so broad (or generic or vague) that it becomes nearly impossible to obtain a meaningful answer. In a good Introduction, the authors meet all 4 of these criteria.

Example 2 is an Introduction section for a report on the same hypothetical narezode-treatment study, to be submitted to a clinical toxicology journal. The Introduction provides enough background material for the reader to grasp the general topic (ethylene glycol) and why it is toxic to humans. The Introduction then transitions to the specific aspect of the field that was studied (narezode treatment for ethylene glycol poisoning) and an explanation of why it is important (narezode is potentially safer than traditional ethanol treatment). The Introduction then finishes with a clear question (whether intravenous narezode would attenuate the metabolic acidosis and renal tubule damage associated with ethylene glycol poisoning). This Introduction is short but still satisfies the 4 criteria described above.

MATERIALS AND METHODS (STUDY DESIGN, EXPERIMENTAL)

The results and conclusions of a study are only as valid as the strength of the methods and study design. The long-term validity of a study also relies on the ability of others to confirm the work, which also requires rigorous and properly documented methods.

Errors of omission (insufficient detail) are common in Methods sections *(12)*. As a peer reviewer, you must rigorously evaluate the information presented about the methods and experimental design. Even if you have expertise in only selected portions of the study (e.g., analytical vs clinical content), if you do not understand some aspect of the methods, let the editor know in your review that you question whether sufficient detail was provided. The editor can then act accordingly. Two examples below illustrate the potential impact of missing experimental details.

One example is a manuscript that describes an analytical method for a diagnostic biomarker. Although authors are usually good about providing such details as the concentrations of special solutions, volumes of sample used, the steps involved in performing an assay, and instrument parameters, they sometimes fail to include potentially important information, such as biomarker stability, the age/condition of specimens used to validate the diagnostic accuracy of the assay, how patient diagnoses were made, and even receipt of approval by a human subject review committee for the use of biological specimens.

A second example is the clinical study of a diagnostic biomarker. In this type of study, authors are generally good at including descriptions of patient populations and patient selection, diagnostic criteria, treatment protocols, approval of human or animal experimentation, the type of study, and outcomes assessment. Yet, they may not recognize the importance of describing specimen handling or analytical details because they might assume these details to be secondary to the clinical details or not recognize them as major contributors to the results obtained during the study. In some medical journals, the Methods/Experimental section is relegated to the end of the paper, thereby placing a greater focus on the Results and Discussion sections that precede it. Other journals print only a short general summary of the methods at the end and require readers to refer to online supplements. A recent appeal *(13)* to the International Committee of Medical Journal Editors stressed the importance of a full description of laboratory methods and specimen handling in clinical-study reports. For studies that use commercial diagnostic tests, the actual name and generation of the assay, the manufacturer, and the instrument used for analyses should be provided in the manuscript. Additionally, performance characteristics (e.g., assay imprecision), reportable range, and reference interval used in each investigator's laboratory should be provided.

Equally important to how an experiment was performed is why it was performed. If it is not clear from the text why the authors performed a specific experiment, added a reagent, selected a patient population, or used a certain statistical analysis, ask that this information be added so that readers can better understand the study.

RESULTS

The 2 criteria that you should use to judge the results are (*a*) whether the results answer the question or hypothesis stated at the beginning of the manuscript, and (*b*) whether the quality of the results is sufficient to support the answer.

The results of the study should be presented in a clear and unbiased manner. The presentation should follow the experimental or chronological order of the Methods section. It should be easy for you to link the text describing an experiment to the text that presents the corresponding results. Make sure that results are reported for every experiment.

Similarly, the authors should present data that explain or support every result. Data are usually presented in tables and figures; what the data show is summarized or explained as a result in the text. The tables and figures, aided by properly created legends, should be clear enough that you are able to understand the message without referring back and forth to the main text *(14)*. For graphs and pictures, the image quality should also be high enough that all important features will still be readable once they are reduced to final print size. The data in a table or figure should not be repeated in the text unless the table or figure includes a very large amount of data, in which case the author may need to highlight 1 or 2 key pieces of data in the text.

The individual sections of any multipart figure or table must relate back to a common experiment. To stretch the limits on the allowed number of figures and tables, authors might attempt to sneak in a figure by creating a multipart figure or a large, complex table. As a peer reviewer, you should not hesitate to request that a large table or figure be split into 2 separate tables or figures.

Take a hard look at the numbers presented in the Results section. Perform a random check to verify that the numbers in tables, bar graphs, pie charts, or other displays add up and whether they match the numbers in the Methods section. For example, the Methods section might state that 25 patients were evaluated, but the Results section shows data for 24 patients. If the numbers do not add up, ask why. Perhaps a patient was excluded from the study or lost to follow-up. There may have been a dropout or an inconclusive result or diagnosis. Even if not included in the final analysis, all data should be accounted for.

Evaluate whether the statistical methods used to analyze the data are appropriate. Remember that there is a difference between statistical significance and clinical or practical significance *(5)*. Do not let a *P* value

<0.05 convince you that the results must be important. Similarly, do not allow authors to draw unwarranted attention to nonsignificant findings by describing the results as "trending toward" or "tending to show." If you are not familiar with any aspect of the statistical methods, tell the editor in your review that this section of the manuscript should be referred to a biostatistician if the editor has not already done that.

DISCUSSION

The purpose of the Discussion section is to explain what the results mean and what contribution the paper makes to the field of study *(15)*. If the Discussion section is not convincing about the meaning and importance of the findings, it does not really matter how the experiments were performed or what results were reported.

The Discussion section should start by clearly presenting the answer to the question, hypothesis, or goal of the study. The authors must then show how the answer is supported by the results. Each experiment described in the Methods section should contribute to the answer, and each associated result should also contribute to the answer. The authors should be able to describe how their results are supported by other studies and how their results support other studies. Any surprising findings or results that differ from previously published work must also be addressed. Authors must describe limitations to the study and whether these limitations might have affected the results. The interpretation of the results should be balanced and include any other possible explanations for the findings.

Two ways that authors stumble when preparing the Discussion section are by repeating many of the details just presented in the Results section and by repeating the Introduction and all of the background material in it. If you see a lot of repeat of the results or introductory material you should question why the authors emphasized this information. Do they have nothing else to say about the significance of their findings?

Lastly, consider the authors' conclusions or summary statements. There is no room for conjecture or opinion here by the authors. All conclusions must be valid and supported by the data. The conclusions must relate directly to the original question, hypothesis, or goal. It is especially important that the conclusions not extend beyond the scope of the study or beyond what the data and results support.

Example 3 shows an example Discussion for the study and manuscript described earlier in Examples 1 and 2. Note how the Discussion starts by restating the original question and then presents the answer that was obtained. The second and third paragraphs show how the answer is supported by the results. The fourth paragraph describes how the results of the submitted study are supported by other studies. The fifth paragraph makes note of a limitation of the study, which was that long-term follow-up was not possible for $>50\%$ of the patients. Finally, the authors' conclusions in the summary paragraph must relate directly to the original question and not make any claims beyond the scope of the study.

REFERENCES AND CITATIONS

It is not your job as a peer reviewer to check the accuracy of every citation in the text or every literature reference; however, you can look for a few things that can give you an idea of the authors' knowledge of the literature and whether the authors have cited the literature appropriately. Be wary if books or book chapters are heavily cited, because that can be a sign that the authors have not thoroughly evaluated the literature, especially the current (up-to-date) literature. In addition to being current, the literature cited in the manuscript should be balanced and not ignore a particular hypothesis or point of view that might differ from that of the authors. Do a random check to see if the references appear to be accounted for in the manuscript. For example, if there are 40 references in the list at the end of the manuscript, is the number of citations in the manuscript also 40 in number?

If the authors cite a manuscript as being "in press," request that the authors supply a copy of the article so that you can judge how that particular study relates to the one submitted for your review. Look for overlap between the 2 documents in the methods, results, figures, and tables. The manuscript you are peer reviewing should be novel and independent of the article in press. Be aware of authors who split larger studies into numerous smaller studies and send you the "minimal publishable unit." Lastly, do not allow authors to cite unpublished data/results, manuscripts that have been submitted but not accepted, or manuscripts in preparation. With few exceptions, if the authors want you to believe that unpublished results belong in the manuscript, ask yourself why the authors can't supply the results in a supplemental electronic file. You (the peer reviewer) and the editor can then decide whether such results need to be included. Nonaccepted manuscripts or manuscripts in preparation might never be accepted and published and therefore should not be considered as part of the citable literature until they are published. Ask authors to remove any reference to these types of manuscripts.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting*

or revising the article for intellectual content; and (c) final approval of the published article.

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Example 1.[1]

Intravenous Narezode Added to Dialysis Reduces Ethylene Glycol Toxicity in Humans

BACKGROUND: Ethylene glycol (EG) ingestion produces intoxication, metabolic acidosis, and potential renal failure. The major toxicity arises from the alcohol dehydrogenase–mediated metabolites glycolic acid and oxalic acid. Thus, minimizing metabolite formation is important. The enzyme-blocking agent narezode, added to dialysis, has been tested in dogs with success but has not yet been tested in humans. We investigated whether intravenous narezode would attenuate the metabolic acidosis and renal tubular damage associated with EG poisoning in humans.

METHODS: After confirming EG ingestion by gas chromatographic analysis of blood, patients were divided into 2 treatment groups (dialysis/intravenous 10% ethanol, n = 23, and dialysis/intravenous narezode 10 mg/kg, n = 21). Blood pH and urinary oxalate and α_1-microglobulin (a biomarker of renal tubule damage) excretion were monitored for 48 h. Patients were also monitored for allergic reactions to narezode (e.g., respiration, temperature, shaking).

RESULTS: When started within 6 h after EG ingestion, dialysis/narezode reduced urinary oxalate excretion by 86% and the frequency of metabolic acidosis (blood pH, <7.35) by 85%, compared with dialysis/ethanol. Urinary excretion of α_1-microglobulin was decreased by 95% compared with dialysis/ethanol. No allergic side effects were observed in narezode-treated patients.

CONCLUSIONS: The decrease in the incidence of oxalate formation, metabolic acidosis, and renal tubule damage when narezode was used to treat EG poisoning, plus the apparent lack of side effects in our patients, supports the addition of this competitive inhibitor to treatment regimens for EG poisoning.

[1] Reference numbers do not correspond to any of the references at the end of this paper.

Example 2.[1]

Ethylene glycol (EG) is an odorless, colorless, syrupy liquid that is commonly used as an antifreeze agent and in deicing solutions for aircraft. Owing to its sweet taste and its ability to induce intoxicating effects similar to those of ethanol, EG may be accidentally or intentionally ingested *(1–3)*. Unfortunately, EG ingestion carries a clinically significant risk of mortality and morbidity by causing damage to the central nervous system, heart, and kidneys *(4–7)*. The major toxicity from EG ingestion arises from its alcohol dehydrogenase–mediated metabolites, glycolic acid and oxalic acid *(8)*. Minimizing metabolite formation is therefore an important component of the patient's medical treatment.

In the past, intravenous ethanol has been added to the treatment regimen because ethanol competes with EG as a substrate for alcohol dehydrogenase *(9–11)*, thereby reducing the alcohol dehydrogenase–mediated metabolism of EG. Unfortunately, ethanol has several disadvantages, which include the need for constant infusion to maintain effective blood concentrations of 100–150 mg/dL, the need to monitor blood ethanol concentrations every 60–90 min, and the side effects of these high ethanol concentrations. Thus, alternative antidotes have been sought.

Narezode (6-methylpyrazole) is a known competitive inhibitor of alcohol dehydrogenase *(12–14)* that could substitute for ethanol in the treatment of EG poisoning. Potential advantages of this agent include fewer side effects compared with ethanol and no need to monitor blood concentrations. Studies in dogs have shown that this enzyme-blocking agent, when added to dialysis, appears not only to inhibit the alcohol dehydrogenase–mediated EG metabolism *(15, 16)* but also to help lessen the metabolic acidosis and organ damage associated with EG poisoning *(17)*. However, no studies have been performed in humans to show similar positive effects. Therefore, in this study we investigated whether intravenous narezode would attenuate the metabolic acidosis and renal tubule damage associated with EG poisoning in humans.

[1] Reference numbers do not correspond to any of the references at the end of this paper.

Example 3.[1]

In this study, we investigated whether intravenous narezode would attenuate the metabolic acidosis and renal tubule damage associated with EG intoxication. Our results show that narezode, when started 6 h after EG ingestion, can greatly reduce the degree of metabolic acidosis and renal tubule damage associated with EG poisoning in humans.

The EG metabolite oxalic acid in sufficient concentrations can cause renal tubule damage. Our first finding that dialysis/narezode can decrease renal damage is supported by our measurements of urinary oxalate excretion, which was greatly reduced compared with dialysis/ethanol. Our finding that narezode can decrease renal damage is also supported by the large reduction in the urinary excretion of α_1-microglobulin, a biomarker of renal tubule damage.

Our second finding that narezode/dialysis decreases the degree of metabolic acidosis is supported by our inline blood pH measurements, which showed a large reduction in the number of patients who had a blood pH value <7.35.

Evidence of a competitive effect of narezode on EG metabolism by alcohol dehydrogenase comes from the work of Proctor and Schlesser *(18)*, who showed that, in healthy volunteers, oral narezode significantly reduced the rate of elimination of moderate doses of ethanol, which is also metabolized through alcohol dehydrogenase. Two studies *(19, 20)* have demonstrated that, in monkeys, narezode can inhibit methanol metabolism to formate, which is also mediated by alcohol dehydrogenase.

A limitation to interpreting long-term success was that 12 of the 21 patients who received narezode and 13 of the 24 patients who received ethanol did not complete the 6-month follow-up, and so we could not evaluate whether there were any long-term changes in renal function.

In summary, our demonstration that narezode decreases the incidence of oxalate formation, metabolic acidosis, and renal tubule damage when used to treat EG poisoning—plus the apparent lack of side effects in our patients—supports the addition of this competitive inhibitor to treatment regimens for EG poisoning.

[1] Reference numbers do not correspond to any of the references at the end of this paper.