Reviewer's report

Title: Validation of a Transparent Decision Model to Rate Drug Interactions

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Reviewer: Philip Hansten

Reviewer's report:

General Comments:

This paper addresses a vitally important issue in the rational use of drug interaction information in the clinical setting. I believe this paper represents an important advance in the development of classification systems for drug interactions for the following reasons:

1. The transparency of the decision model is important. This means that people working in the field (as well as users) will be able to understand how the decisions are made, and it should provide a framework for people working in different centers to communicate effectively. This could be a real advance in the field of drug interactions.

2. The authors selected appropriate questions for the decision model. They addressed the factors that are important in the assessment of the clinical importance of drug interactions in the clinical setting.

3. I ran several drug interactions through their decision model, and I think the model could be developed into an excellent method for categorizing drug interactions for the product information. For example, colchicine plus clarithromycin would be a “DM-E” instead of merely being a strong caution as is currently the case in the US product information.

4. On page 11, the authors state their belief that “…suitable alternatives or necessary complex monitoring is reason enough to avoid the combination.” I agree completely, and feel that their decision model is better at considering this than other systems of categorization, or, for that matter, decisions made by individual practitioners.

Discretionary Revisions:

p. 5: Under part "a" of the First Question (AIA), it might be worthwhile to add "credible" studies or reports. Some case reports are not credible, and should be excluded.

p. 5: Question #2, it might be good to explain what is meant by "normal patient population." For example, the risk of serious hyperkalemia from combined use of ACE inhibitors and spironolactone is much greater in elderly patients with diabetes and significant renal disease. Would they be considered the “normal patient population?”
p. 5: Question #3: Would “counter-measures” be better than “precautionary measures” in this case? “Precautionary” might sound more like something you do to prevent the interaction, rather than something to counter the effects of the interaction outcome.

p. 6: Question #5 (part “a”): If possible, it might be good to have this question sooner in the series of questions, since (as the authors stated) suitable alternatives make the decision to avoid the interaction much easier. I’m not sure how easy that would be to move it earlier, so they may need to leave it here as is.

p. 6: Question #5 (part “b”): Here I think “credible” should be added in front of “dose adjustments” because—at least in the US—the product information sometimes provides questionable dosage adjustment guidelines. For example, for colchicine, a “one-size-fits-all” dosage adjustment is recommended in the product information that would almost certainly result in some patients having subtherapeutic colchicine concentrations, and other having serious colchicine toxicity. The way the question reads now, I would have to answer “yes” that there are guidelines…but they are not credible guidelines, so the answer should actually be “no.”

p. 7: Validation: This looks like a good initial attempt at validation, and it does appear that the decision model fit well with the ratings of the clinical pharmacologist. Additional validation, perhaps with several clinical pharmacologists or other drug interaction experts, might be useful in the future. Perhaps this study will stimulate people in other centers to validate the decision model.

I am not good at this kind of statistics, so I think the editors should decide if getting a statistical evaluation is necessary. It may be very straightforward, and no additional statistical evaluation is needed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

The only possible financial competing interests that I have are the current and ongoing publication of 2 drug interaction books:

2. Hansten PD, Horn JR. The Top 100 Drug Interactions. A Guide to Patient