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Pharmacoepidemiology and in silico drug evaluation: is there common ground?

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Shortcomings of randomized trials have long been recognized by medical researchers (1,2). These shortcomings include a reduced range of risk factors for the outcome among patients enrolled in pre-approval trials. The reduced range enhances the validity of the trials, but the patient populations are highly selected compared with the broad range of risk factors represented among patients who are eventually treated with the drug. This restriction may reduce the generalizability of the findings from those studied to those with different baseline risks.

Given the reality that randomized trials will not be able to provide answers to all questions we might wish to pose, researchers and regulators alike should be highly motivated to find alternative strategies for understanding how drug effects vary across patient populations. Pharmacoepidemiology provides one such approach; in this issue, Boissel at al. demonstrate another approach, using numerical models and simulations to model drug effects (3).

Some of the insights offered by Boissel at al. are old news in epidemiology. For example, epidemiologists know that the strength of association in the data typically depends on the prevalence of other causes of the outcome (4). Weak associations tend to be stronger in people who are at low risk (5). Furthermore, epidemiologists know that the scale of measurement can make a difference. For a given value of relative risk, effects of drug treatment that are measured as risk difference or number needed to treat will be less pronounced if the risk among untreated is low and more pronounced if the risk among untreated is high (6). Epidemiologists do not usually assume that a treatment effect is constant over all possible baseline risks. Indeed, it is well recognized that constant treatment effects on one scale of measurement usually imply non-constant treatment effects on another scale (6,7). Discovery of how treatment effects vary by baseline risk is one of the important contributions of post-marketing surveillance of drugs (8). Thus, inconstancy of treatment effects can be readily explained without invoking pharmacokinetic and pharmacodynamic models.

Boissel at al. come to similar conclusions regarding the dangers of extrapolating treatment effects from randomized trials to populations with different baseline risks (3). Their statement of the problem is couched not in epidemiologic terms, but rather in terms of pharmacokinetic and pharmacodynamic effect models. Many parameter values used in their simulations of these models seem to be derived from observation, which is a strength (9). They simulate the protective effect of a drug on the risk of a given disease over the whole range of possible risks from 0 (no risk) to 1 (everyone gets the disease) in the unexposed. In two of the three different effect models that they used, their simulations showed that risk in those exposed to the drug

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was not a constant fraction of the risk in the unexposed over the range of unexposed risk. They concluded that this variability should be taken into account when discovering and developing new drugs.

We think that their conclusion is reasonable, in large part because it can also be deduced from the basic epidemiologic considerations outlined above. Boissel et al. do not discuss basic notions of measurement scale and its influence on the constancy of treatment effects, nor do they provide much detail regarding the parameters and model structures used in their simulations. Simulation results are, however, always dependent on the details of the models used to simulate the data (9,10). For example, the main conclusion of Boissel et al. is based on the concave upward shape of the data in their figures 3 and 4 (3). This shape might be no more than an artefact of their modeling constraints that the treatment loses efficacy as the risk for the outcome increases to 1. This constraint would be understandable for an exposure that increased, rather than decreased risk, because if the risk among unexposed is already 100%, the exposure cannot increase it further. Their model, however, examined exposures that decrease risk, a situation in which it makes little sense to suppose that if risk among unexposed is 100%, the exposure cannot reduce it.

Despite this reservation, we are encouraged to see exercises that can contribute to a sharper understanding of what to expect when drugs are given to different patient populations. Modeling, which is the “in silico” approach (in contrast to in vitro and in vivo), can be illuminating. Pharmacoepidemiology could profit from taking into account pharmacologic knowledge regarding factors that can increase or decrease the bioavailability of a drug and enhance or inhibit its effects. Specifically, insights about such factors obtained from pharmacokinetic and pharmacodynamic models can inform pharmacoepidemiologists about which factors should be included as effect-measure modifiers in epidemiologic analyses. Such models might lead pharmacoepidemiologists to hypothesize that the likely relevant exposure is not the drug per se but the plasma level of active drug or metabolite. For example, benzodiazepines might have a more pronounced effect on the risk for hip fracture when used in combination with drugs known to interact with benzodiazepines pharmacodynamically (11). Reciprocally, in silico evaluation of drugs (3,12,13) could benefit from epidemiologic thinking by incorporating basic principles of measurement scales, effect-measure modification, confounding, and modeling strategies (6). Between the two approaches, there is some common ground, starting with the shared concern about the ability to predict, from the results of randomized trials, what a new drug will do to the health of the public (14).

References

1. Avorn, J. Powerful medicines: the benefits, risks, and costs of prescription drugs. New York: Knopf; 2004.
2. Strom, BL., editor. Pharmacoepidemiology. 4. Wiley & Sons;
3. Boissel, et al. New insights on the relation between untreated and treated outcomes for a given therapy. J Clin Epidemiol. in press
4. Rothman KJ. Causes. Am J Epidemiol 1976;104:587–92. [PubMed: 998606]
5. Rothman KJ, Poole C. A strengthening programme for weak associations. Int J Epidemiol 1988;17:955–9. [PubMed: 3225112]
6. Rothman, KJ.; Greenland, S., editors. Modern Epidemiology. 2. Philadelphia: Lippincott Williams & Wilkins; 1998.
7. Stürmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. Pharmacoepidemiol Drug Saf 2006;15:698–709. [PubMed: 16528796]

8. Institute of Medicine Committee on the Assessment of the US Drug Safety System. The future of drug safety: promoting and protecting the health of the public. National Academy Press; Washington DC: 2007.

9. Maldonado G, Greenland S. The importance of critically interpreting simulation studies. Epidemiology 1997;8:453–6. [PubMed: 9209864]

10. Stürmer T, Schneeweiss S, Rothman KJ, Avorn J, Glynn RJ. Performance of propensity score calibration--a simulation study. Am J Epidemiol 2007 May 15;:165, 1110–8.

11. French DD, Chirikos TN, Spehar A, Campbell R, Means H, Bulat T. Effect of concomitant use of benzodiazepines and other drugs on the risk of injury in a veterans population. Drug Safety 2005;28:1141–50. [PubMed: 16329716]

12. Muzikant AL, Penland RC. Models for profiling the potential QT prolongation risk of drugs. Curr Opin Drug Discov Devel 2002;5:127–35.

13. Pappalardo F, Lollini PL, Castiglione F, Motta S. Modeling and simulation of cancer immunoprevention vaccine. Bioinformatics 2005;21:2891–7. [PubMed: 15817697]

14. Avorn J. The marketplace can't give us the drug safety data we need. MedGenMed 2007;9:29. [PubMed: 17435636]