

Discussion of “Multivariate Bayesian Logistic Regression for Analysis of Clinical Trial Safety Issues” by W. DuMouchel

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Drug safety is a major medical concern. Appropriately so. And recent high profile cases have heightened the level of concern. These cases include Vioxx [2], Vytorin and its components [3], Tysabri [4] and Avandia [5].

These and other cases and the controversies they have engendered have increased awareness that dealing with and understanding drug safety issues is enormously difficult. No doubt the final verdict has been wrong in some cases (not necessarily any of the ones mentioned above). Drugs are not protected by the “innocent until proven guilty” principle. Just as with national security measures, heightened awareness is good, but overreaction can be detrimental to delivering good medicine.

Inferential problems related to drug safety are numerous as well as difficult. First, there are many types of serious adverse effects to consider. Drugs can kill or induce potentially fatal conditions. They can also lead to one or more effects that detract from the patient’s quality of life. Multiplicities abound. Moreover, the same effects usually occur naturally, perhaps even as part of the disease process for which the drug is being used. The statistical question is whether and which serious adverse effects occur at an increased rate for patients taking the drug.

The medical questions are also difficult. All drugs cause some side effects, usually in a dose-dependent fashion. So the issue is the benefit/risk trade-off. For example, the same serious adverse effect can have a very different implication in treating cancer, say, than in the primary prevention of cardiovascular events. Indeed, for some cancer therapies, certain adverse effects are a good thing because they indicate that the therapy

is doing a better job of fighting the tumor: “Congratulations, Ms. Smith, your hot flashes mean the drug is working!”

Compounding the multiplicity of types of adverse effects is the multiplicity of drugs, their doses, and combinations. For any particular adverse effect upon which no drug has an impact, the data will show that half of the drugs have some amount of increase in the incidence of that effect. And some of these increases will be statistically significant. A small proportion of the drugs will be shown to be detrimental statistically in any particular comparison, but there are many comparisons. How to separate the signal from the noise? And how to balance false positives (rejected drugs that are safe) with false negatives?

Bonferroni and other traditional adjustments for multiple comparisons are inappropriate when the measurements concern safety (and they may never be appropriate!). They are used to protect against rejecting too many null hypotheses. When the question is one of safety, this would mean the more comparisons one makes, the more difficult it is to determine that a drug is unsafe.

Bill DuMouchel has a long history of developing and using Bayesian hierarchical modeling methods for addressing multiplicity problems associated with large, sparse databases. His data mining approaches as applied to questions of drug safety have been used by the U.S. Food and Drug Administration, among others. The methodology he has previously developed gives a clear view through muddy waters. His article in this issue makes the view even clearer.

DuMouchel’s application of multivariate Bayesian logistic regression (MBLR) “borrows strength” in the usual Bayesian hierarchical modeling sense. For example, if a drug seems to increase both nausea and vomiting, then the conclusion about both adverse effects is stronger than if either were considered by itself. On the other hand, if the incidence of nausea is elevated

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but that of vomiting is not, then any conclusion about nausea based on all the evidence is less compelling. The borrowing is across clinical trials as well as across related side effects.

Neither aspect of the borrowing in MBLR is novel on its own. Bayesian hierarchical modeling is a standard approach to meta-analysis. And borrowing hierarchically across side effects within body systems has been proposed previously [1]. But putting the two together is novel. And it is an important concept. There are usually many clinical trials conducted of a drug, most with the primary focus on efficacy. It is important to take advantage of all the evidence. Safety applies to the drug and not to the trial. A safety signal may be observable only over several trials. DuMouchel's methodology is consistent with the synthetic nature of the Bayesian approach.

This elegant article with its methodology is a welcome addition to this important problem area. MBLR

will become a standard method for determining whether a drug increases the incidence of any adverse drug effects. It will also provide appropriate estimates for any increases.

REFERENCES

- [1] BERRY, S. M. and BERRY, D. A. (2004). Accounting for multiplicities in assessing drug safety: A three-level hierarchical mixture model. *Biometrics* **60** 418–426. MR2066276
- [2] <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm>.
- [3] <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm162899.htm>.
- [4] <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm182667.htm>.
- [5] <http://www.fda.gov/Drugs/DrugSafety/ucm241411.htm>.