



Who Speaks for the Prescribing Physicians?

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Nobody does, unfortunately.

- 1) NDAs seem to be designed to maximize chances of approval, with careful selection of subjects who are likely to benefit and exclusion of those likely to have adverse effects, in pivotal clinical trials.***
- 2) After approval, promotion and marketing efforts are aimed at maximizing prescription for use, in patients not always similar to those studied in the trials upon which approvals were based.***
- 3) Responsibility for detecting and reporting adverse effects in patients falls upon prescribing doctors who have no resources or motivation to do so.***



Nobody does, unfortunately.

- 4) *Warnings and limitations are put into long and complex labeling that is difficult for patients, and even some doctors, to understand, read, or follow.*
- 5) *Direct-to-consumer advertising and promotion are incessant, and diminish the ability of the physician to advise the patients, who just demand the drug.*
- 6) *Responsibility for post-approval follow-up and reporting is misplaced on the doctors, and should be considered for the sponsoring company that is marketing the product aggressively.*



Nobody does, unfortunately.

- 7) *Reliance on the published literature is misplaced and does not, cannot, reflect the full extent of exposure. It is important to learn how many do NOT show bad effects, but that is unpublishable usually, unless a fully balanced report is made.*
- 8) *Even though serious drug-induced toxicity is rare, there is so much use of drug and so-called dietary supplements that they are the leading cause of acute liver failure in the United States (Lee at al.)*



Looking Ahead into the Clouds

- 1) Great efforts are expended looking for magical new biomarkers that will “diagnose” DILI. Even one.**
- 2) The problem is that what is being looked for is not one discrete disease but a vast spectrum of them.**
- 3) We earlier had an opportunity to find a biomarker for one disease, viral hepatitis B, in which searching for a serum protein associated with leukemia, Down syndrome, and blood transfusions led to change of Au (Australia antigen) to HBsAg (the coating of the virus itself), and subsequently to the distinction of non-A, non-B = C virus.**



Looking Ahead into the Clouds

- 4) *Search for a new and better biomarker would be nice if it worked, but it hasn't for many years, and may be just an oversimplification of a problem that is not simple.*
- 5) *We may have to look into the “clouds,” the gigantic arrays of data that can be and are being collected for analyses, and some new thinking.*
- 6) *We are sloppy with our language in comparing risks and benefits. They are not comparable; risk is a chance or probability; benefit is a good effect. We should compare the chances of good effects to the risks of bad effects. This is not just semantics.*



Looking Ahead into the Clouds

- 7) *Sloppy language reflects sloppy thought. Terms such as “benefit risk ratio”, or its inverse, are poor and dangerous terms, for either good effects or bad effects of drugs may be zero or close to it, leading to ratios approaching infinity. Just use differences.*
- 8) *We need to learn how many patients are affected how much by drugs or dietary supplements, how rapidly, for how long, how likely due to the drug.*
- 9) *These remarks are intentionally made to stimulate objections and discussion, debate and possible resolution or consensus.*