Presentation Outline

Many steps in the current system favor identification of drug benefits over drug harms.

- Post-marketing surveillance approaches and regulatory approaches are inadequate (relevant to recent VIOXX case). Need other approaches or change in approach.

- Funding disparities for studying risks vs. benefits

- Funding sources make for experts in benefits: Relevance to academic thought leaders and, ultimately, treatment guidelines

- For some drugs, benefits may be targeted e.g. to one organ system (easy to study) and harms may be of similar (or greater) total magnitude but distributed across causes (harder to study).

- Human subjects’ regulations provide for (well-intentioned and necessary) obstacles in studying risks vs. benefits. So, for example, populations at risk of harm are excluded from the trials, so the outcome of those trials does not show, as claimed, an absence of harm.

Selection criteria for clinical trials actively (if inadvertently and with good reasons) work against identification of Adverse Effects (AEs).

- The problem arises when absence of evidence is interpreted as evidence of absence of AEs, and the findings are generalized to a much broader group with a different and less favorable risk-benefit profile.

- The character of evidence of relevance to AEs may be difficult to publish (observational studies).

- Interpretations in literature often favor benefit, unjustifiably.

Publication bias related to drug-funded studies

- Lack of open access to data from pharmaceutical-funded studies (cases where this is relevant)
• If published, strong media attention to benefits vs. risks (industry ensures we hear about the former; no corresponding interest group to ensure we hear about the latter).

Together features of the current drug approval system “stack the deck” providing an unbalanced representation of risks vs. benefits.

Summary of Discussion
1. How best to “fix” the drug approval system? What can be done to make the process more balanced?

   • Lawsuits
     Unfortunately, the public has been disarmed by recent legislation that will not allow states to consider class-action suits. Requirements that such actions go through federal courts makes them much more difficult to handle.

     Drug companies are immune from lawsuits for negative side effects. It is the physicians who are sued.

   • Guidelines requiring risk-benefit analyses by epidemiologists not themselves expert in the subject area under study, e.g., statins, hence not “invested” in one outcome or another.

   • Changes at the FDA
     Permit lower standards of evidence for (potential) harms.

     Tracking of inconclusive results, or partial evidence, so clinicians and patients are fully informed about potential problems.

   • Better medical training in trial design and data assessment; greater awareness of effect of industry-academic ties, conflicts of interest; integrity issues.

2. How much are physicians themselves complicit in the under-reporting of adverse effects?
   • Links to industry that compromise objectivity

   • Practice of prescribing drugs for “off label” uses or to patient populations significantly different from study populations.

3. Mustn’t we also balance the risk of missing adverse effects during clinical trials with the risk of slowing down or preventing drug development?
4. Important to distinguish
   • Immoral behavior, clear conflicts, drug company marketing “games”
   • Unintended bias, e.g., against negative or non-results
   • Structural problems, e.g., having the same agency monitor long term safety on drugs they approved.

   Each of these requires a different solution or approach.