BENEFIT RISK RATIO

Aditya Patankar1, Abhinav Paknikar1, Atul Laddu1, Fakiha Siddiqui2, and Jawed Fareed2
1=Global Thrombosis Forum, Suwanee, GA, USA
2=Loyola University, Chicago, IL, USA

Introduction

All drugs produce a range of effects, both therapeutic and adverse. A risk-benefit ratio (or benefit-risk ratio) is the ratio of the risk of an action to its potential benefits. Risk-benefit analysis (or benefit-risk analysis) is the analysis that seeks to quantify the risk and benefits and hence their ratio.

The risk-benefit ratio is a crucial concept that weighs the estimated harm (adverse effects, cost, inconvenience) against the expected benefits (symptom relief, cure, reduced complications).

A drug should only be prescribed when the benefits outweigh the risks. However, this ratio is difficult to quantify precisely for each patient due to variables like the nature and duration of harm, as well as individual patient values. Therefore, clinicians often rely on large-scale data (pharmacoepidemiology) and personal experience.

History

- In the late 1990s and early 2000s, while there was an increasing pressure from regulatory agencies for pharmaceutical companies to perform Benefit Risk (BR) evaluation more routinely and systematically, there were only a few guidelines from the regulators on how to perform BR analyses.
- The majority of the publications in the literature were listings of benefits and risks which might be useful for clinicians but, without taking into account the relative importance of benefits to risks.
- 1998: The need for a more systematic and consistent approach to combining the benefits and risks was first introduced by the Council for International Organizations of Medical Sciences (CIOMS), in the report of CIOMS Working Group IV, Benefit-risk balance for marketed drugs: evaluating safety signals.
- As ordinarily used, therefore, the BR ratio compares figuratively, but not often quantitatively, the relative magnitudes of benefits and risks.
- By 1999, there was still no guidance from the regulatory perspective.
- The European Committee for Proprietary Medicinal Products recommended methods to evaluate risks in the postmarketing settings (such as observational studies).
- Benefit-Risk Action Team (BRAT), a collaborative project on BR evaluation sponsored by The Pharmaceutical Research and Manufacturers of America was initiated, European Medicines Agency (EMA).

Appropriate B-R Ratio

- Risk is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study. Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.
- Benefit applies to the potential of the research treatment to ameliorate a condition or treat a disease. This can apply to an individual participant or to a population. In research as in clinical medicine, results cannot be guaranteed but, as a consequence of prior work, a benefit may appear to be a reasonable expectation. Since this is research, an advantage for the treatment groups cannot be presupposed. Since the risks have not been fully evaluated, a statement of individual benefit should be made most cautiously if at all.

Appropriate B-R Ratio (Contd.)

- A main role of IRBs is to determine the risk versus benefit ratio for clinical studies. It is not ethical to conduct a study in which an individual or a group is labeled so as to be stigmatized or to be made less employable or insurable.
- Blinding refers to a process whereby the participant does not know whether he/she is receiving an active agent or a similar appearing inactive substance or mock procedure.
- Double blinding is a process whereby neither the investigator nor the participant knows which agent the participant is receiving. Usually the research pharmacy holds the master list in case there are complications.

The BRAT Framework

- The BRAT framework is a process to perform BR evaluation in a structured, transparent, and consistent way.
- The process consists of six steps (define the context, identify outcomes, identify data sources, customize framework, assess outcome importance, and display and interpret key BR metrics)
- BRAT helps to inform stakeholders to make BR decisions, to communicate the decisions and the rationales for the decisions, and therefore increases the transparency of the whole process.
- The FDA and the European Committee for Proprietary Medicinal Products of the European Medicines Agency are increasingly requesting benefit-risk analyses of pharmaceutical products.

Problems with the B-R Ratio

- Individual Variability: Due to genetic and environmental factors, the effective dose for some individuals may be toxic for others.
- Efficacy vs. Tolerability: A drug follows the dose response curve for maximal therapeutic effects (Figure 1).
- Pharmacoepidemiology: Clinicians often rely on large-scale data to make informed decisions, especially when the risk-benefit ratio is hard to determine for individual patients, to keep in the therapeutic window (Figure 2, 3).

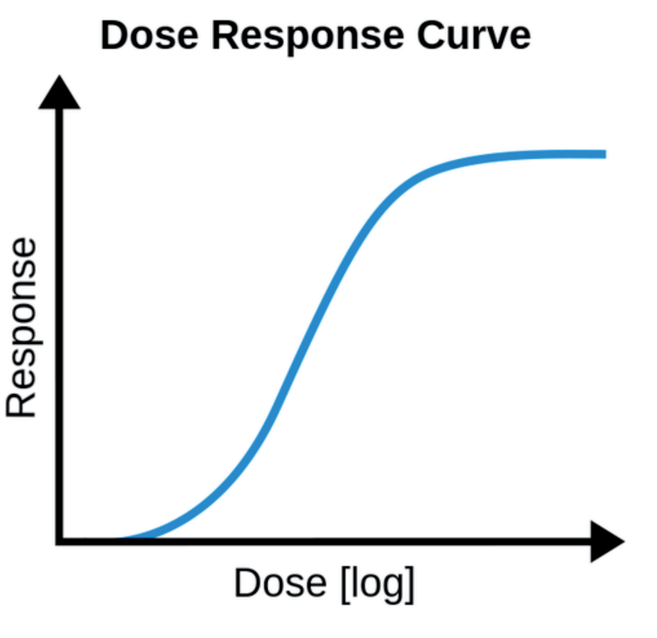

Figure 1: Dose Response Curve

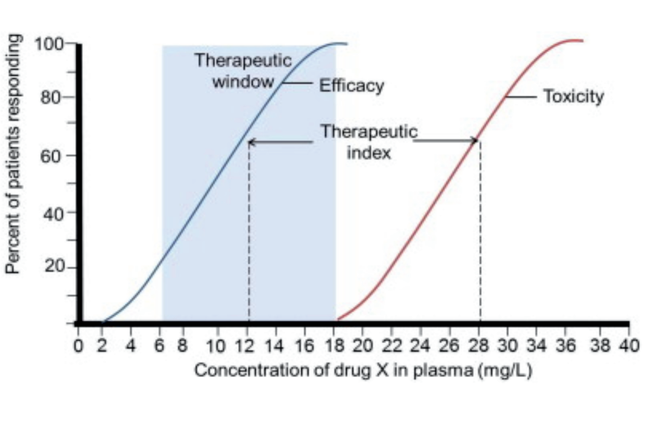

Figure 2: Therapeutic Window

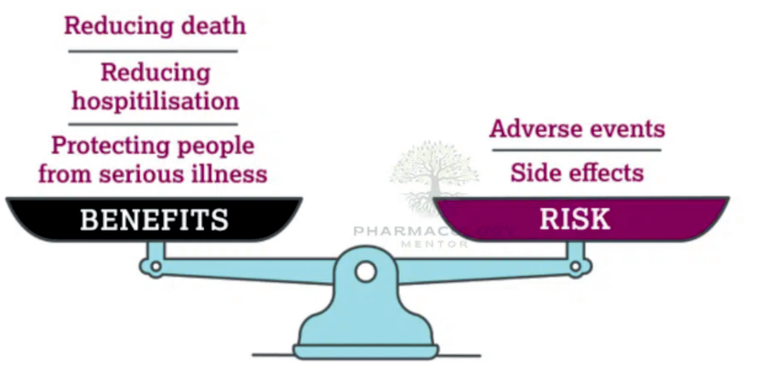

Figure 3: Benefit Risk Ratio

Dabigatran 150 mg Versus 110 mg

- In the RELY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy), 110-mg and 150-mg doses of dabigatran, a direct oral anticoagulant agent (DOAC), a direct thrombin inhibitor, were compared against warfarin in patients with nonvalvular atrial fibrillation.
- Both doses were noninferior to warfarin with respect to the primary efficacy endpoint (stroke or systemic embolic event), but the 150-mg dose was superior to warfarin (an anticoagulant agent) and to the 110-mg dose.
- With respect to the primary safety outcome (major bleeding), the 110-mg dose was superior to warfarin (produced less bleeding), whereas the 150-mg dose was similar to warfarin (produced similar bleeding).
- Despite the favorable benefit-risk balance for 110 mg over the 150-mg, the FDA approved only the higher dose.

Donanemab

- A FDA advisory panel endorsed the experimental Alzheimer's drug donanemab, which showed slowed early stages of the fatal mind-robbing disease.
- The recommendation came despite pointed questions from advisory committee members about the potential side effects, an antibody that removes beta-amyloid that accumulates in the brains of patients with Alzheimer's disease.
- The FDA is not compelled to follow the recommendation of the advisory committee of outside experts, but it often does so.
- During the FDA's Peripheral and CNS Advisory Committee hearing on Monday, the clinical trials showed the drug slowed cognitive and functional decline for people with early stages of the disease.
- The advisory committee unanimously agreed the studies showed that donanemab was effective at treating people with an early stage of Alzheimer's disease, a stage known as mild cognitive impairment. The panel also said the benefits of the drug outweighed potential risks for people with early stages of the disease.

Conclusions

- All drugs have beneficial and harmful effects. To this end, recent efforts have focused on enhancing benefit-risk assessment to improve transparency and consistency in the regulatory decision-making and to improve communication with external stakeholders. The benefit-risk balance is a complex problem of balancing multiple efficacy and safety outcomes, their probability and uncertainty, using value judgments.
- We believe regular applications of a structured benefit-risk assessment, whether qualitative or quantitative or both, enabled by easy-to-understand graphical presentations that capture uncertainties around the benefit-risk metric, could go a long way in promoting familiarity with and acceptance of these methods among regulators, industry sponsors, journal editors, payers, professional societies, and individual physicians and patients.