Benefit-risk Ratio

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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

- Late 1990s and early 2000s: 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

History, contd.

- 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.

- CIOMS recognized that the common practice of BR evaluation at that time was subjective in nature and further mentioned that there were no methods to evaluate BR profiles of medicinal products comparing different treatments with relative merits.

- There are no accepted general methods for deriving a benefit–risk ratio or another composite metric, or for using such measures to compare relative merits of alternative treatments.

History, contd.

- The BR ratio compares 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).
- The FDA provided guidance on the benefits and risks but not on BR evaluation.

History, contd.

- 2000: A few quantitative BR methods exist taking into account the preference weight of benefits and risks. The papers proposed number needed to treat (NNT) and number needed to harm (NNH) to measure the effects for benefits and risks, respectively, and relative value adjusted NNT to not only take into account benefits and risks but also the preference weight of benefits and risks.

- Mid 2000s, the BR evaluation field has shifted toward a more structured and quantitative approach.

- 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 Benefit Risk 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.

- The federal regulations define only "minimal risk."

- *Minimal risk* exists where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Appropriate Benefit Risk Ratio, contd.

- *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.

- A main role of IRBs is to determine the risk versus benefit ratio for clinical studies. They must make sure that the physical risk is not disproportionate to the benefits. When the physical risk is minimal they must determine that psychological and social risks such as stigma are not important. It is unethical to conduct a study in which an individual or a group is subjected to a test drug, or a placebo.

Appropriate Benefit Risk Ratio, contd.

- ***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. Blinding is also used in research to refer to investigators who analyze components of a study such as X-rays or EKGs without knowing the identity and treatment of the participant. "The X-rays were read blind."

- ***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. Over the course of the last 30 years it became apparent that blinding both participants and research teams reduced biases in the results of studies where subjective elements were important. One result that is almost invariably subjective is the adverse event profile. In the absence of blinding very serious biases can occur, potentially making the results of the study unreliable.

BRAT Framework

- BRAT 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 disable and interpret key BR metrics)
- BRAT helps to make BR decisions, to communicate the decisions and the rationale for the decisions, and therefore increases the transparency of the 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

Approach to Benefit-Risk Assessment

Benefit–Risk Framework developed by the FDA that asks 5 relevant questions:

1. “What is the problem?” (Analysis of Condition).
2. “What other potential interventions exist?” (Unmet Need).
3. “What is the benefit of the proposed intervention?” (Benefit).
4. “What is the risk of the proposed intervention?” (Risk).
5. “What can be done to mitigate/monitor those concerns?” (Risk Management).

The structured Benefit–Risk Framework is a foundational component of regulatory decision-making for the Center for Drug Evaluation and Research and the Center for Biological Evaluation and Research at the FDA.

Problems with the risk benefit ratio analysis

- Individual Variability: Due to genetic and environmental factors, the effective dose for some individuals may be toxic for others.
- Efficacy vs. Tolerability: A drug may have high efficacy but may not be tolerable at doses required for maximal therapeutic effect, as seen with prednisolone in bronchial asthma.
- 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.

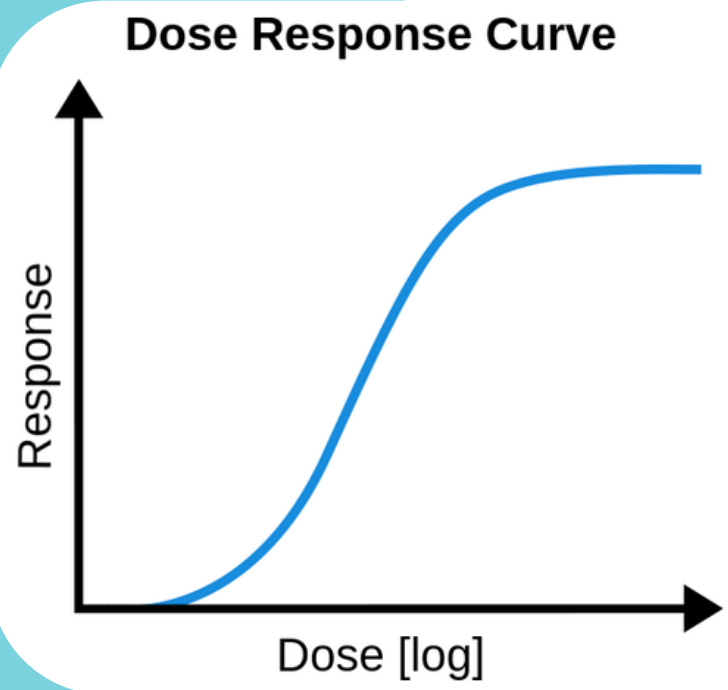

Figure 1: Dose-response curve (DRCs)

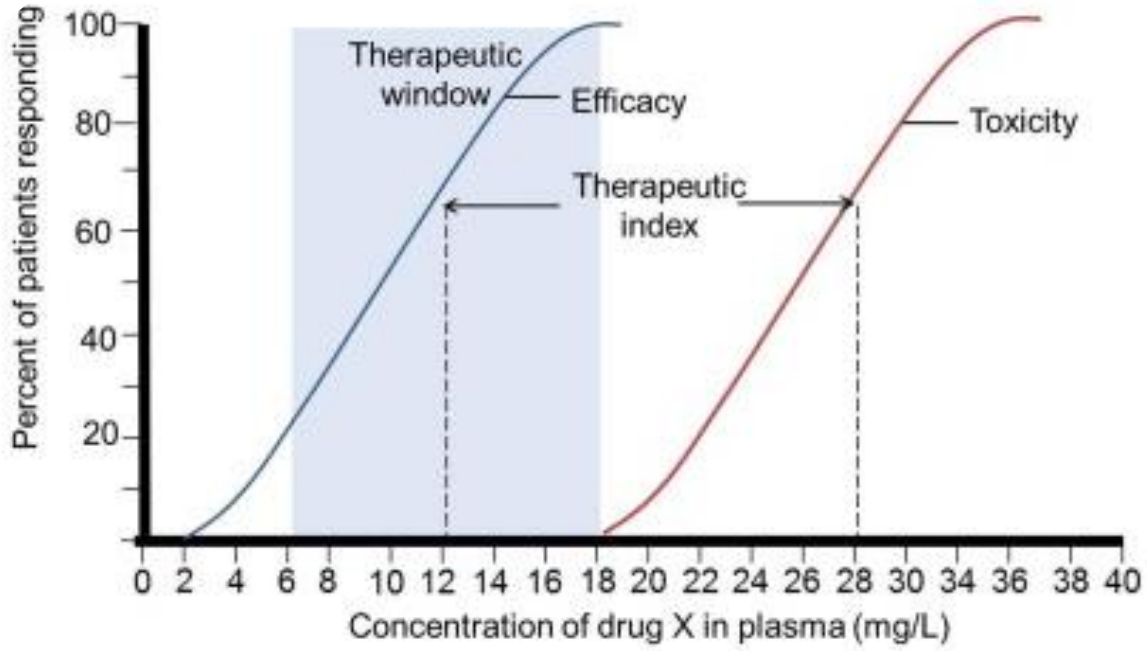

Figure 2: Therapeutic window

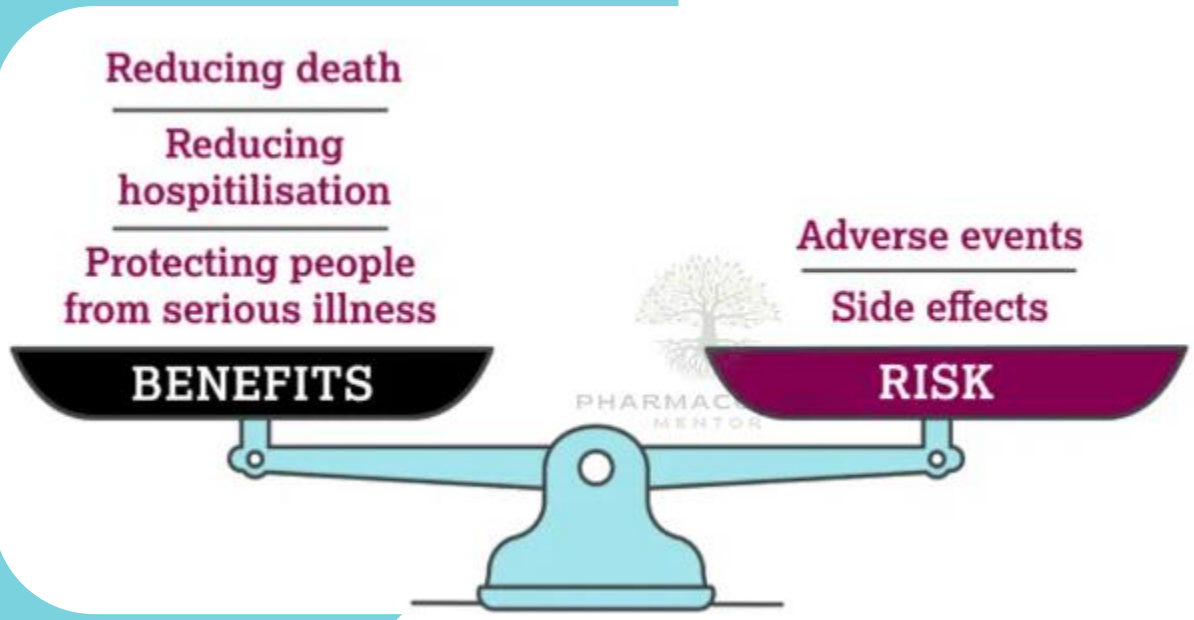

Figure 3: Risk-benefit ratio

Dabigatran 150 mg vs 110 mg

- In the RELY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy), 110-mg and 150-mg doses of dabigatran, 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 and to the 110-mg dose.

- With respect to the primary safety outcome (major bleeding), the 110-mg dose was superior to warfarin, whereas the 150-mg dose was similar to warfarin.

- Despite a favorable benefit–risk balance for both doses, the FDA only approved the higher dose.

Dabigatran 150 mg vs 110 mg, contd.

- The 150-mg dose reduced the risk of stroke, especially disabling stroke excluding hemorrhage (to avoid double counting as an efficacy and safety outcome), more than 110 mg did but also caused more bleeding. Because nonfatal and extracranial bleeding episodes are often less significant than strokes, a disabling stroke should be more heavily weighted.

- Thus, a risk difference of 22 in disabling strokes favoring the 150-mg dose outweighs a risk difference of 26 in severe bleeding favoring the 110-mg dose.

Dabigatran 150 mg vs 110 mg, contd.

- Thus, the favorable benefit–risk balance for 150 mg over the 110-mg dose led the FDA to approve only the higher dose.

- The FDA approved a dose of 75 mg for patients with estimated glomerular filtration rate of <30 mL/min, in whom exposure is increased by 6-fold. This decision was based not on trial efficacy and safety data but on pharmacokinetic and pharmacodynamic modeling.

Transcatheter vs Surgical Aortic Valve Replacement

- Key benefit–risk forest plot for 2 pivotal trials for transcatheter aortic valve replacement (TAVR):
- 1. TAVR: PARTNER 1B (Placement of Aortic Transcatheter Valves) compared with standard medical therapy in patients with severe aortic stenosis who are at prohibitive risk for surgery.
- 2. TAVR: PARTNER 1A (Placement of Aortic Transcatheter Valves) compared with surgical aortic valve replacement in patients who are at high risk for surgery

Transcatheter vs Surgical Aortic Valve Replacement, contd.

- The end point was all-cause mortality at 1 year.
- In PARTNER 1B, TAVR significantly reduced both all-cause deaths and cardiac deaths and hospitalizations but increased stroke, vascular complications, and major bleeding.
- In PARTNER 1A, TAVR was noninferior to surgical aortic valve replacement with respect to mortality (nonsignificant risk difference of 26 per 1000 in all-cause deaths but no difference in cardiac deaths), and it reduced major bleeding but increased stroke, vascular complication, and moderate to severe paravalvular aortic regurgitation.
- Examination of the benefit–risk forest plot clearly shows that although benefit greatly outweighed risk with TAVR in PARTNER 1B, the benefit–risk balance in PARTNER 1A was not as robustly favorable for TAVR.
- The reduction in all-cause deaths with TAVR was nearly 6-fold as great in the former compared with the latter.

Donanemab

- A Food and Drug Administration advisory panel on Monday endorsed the experimental Alzheimer's drug donanemab, which studies 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 of Eli Lilly's drug, 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. A notable exception was when the advisory committee recommended the agency reject Biogen's amyloid-clearing drug aducanumab; nevertheless, the FDA in 2021 approved the drug. Biogen halted sales and gave up ownership of the drug earlier this year.
- During the FDA's Peripheral and Central Nervous System Advisory Committee hearing on Monday, officials at Eli Lilly said 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 outweigh potential risks for people with early stages of the disease.

Donanemab, contd.

- Like other drugs that target and clear amyloid from the brain, studies showed donanemab had side effects that included brain swelling and tiny bleeds that could be detected via MRI.
- At Monday's hearing, Eli Lilly officials said people taking donanemab had a slightly higher rate of MRI-visible injuries, known amyloid-related imaging abnormalities (ARIA), compared with people who took a placebo. Most people who had serious reactions to the drug tended to get them during the first six drug infusions and they decreased over time, Lilly experts said.
- Three people died from ARIA-related injuries during the study, and another two who continued taking the drug after the study finished also died from ARIA injuries. Lilly officials said 2% of people who received donanemab during the study died compared with 1.7% of people who received a placebo.
- Several panel members questioned Eli Lilly experts about the higher risk some patients face who carry two copies of the Alzheimer's susceptibility gene APOE4. Though the panel did not vote on specific recommendations for people who carry two copies of APOE4, some panel members said these patients were at risk of side effects and appeared to benefit less from donanemab.
- Other members of the panel urged Eli Lilly to continue to study the effect of the drug on Black and Hispanic patients, people with Down syndrome and others with a known family risk for the disease.

Donanemab, cont.

- Reisa Sperling, a professor of neurology at Harvard Medical School, testified about the benefits and risks of the drug. She said it's crucial to inform doctors that they should monitor for potential side effects and for doctors to discuss with patients the risks and benefits of the drug.
- She also said side effects are inherent with amyloid-clearing drugs, which appear to be the best-known way to slow Alzheimer's disease progression.
- "We haven't yet hit the full home run," Sperling said. "But right now it is critical to do whatever we can to have an impact to slow this terrible, inexorably progressive disease and allow older people to be able to enjoy this time with their families."
- Michelle Papka, founder and president of the Cognitive and Research Center, a clinical trial site in Springfield, New Jersey, said donanemab is a better option for some patients than the treatments now available.
- "Donanemab is not a miracle cure. It does not stop cognitive decline," Papka said. "But it could be part of an effective cocktail, and we've got to start somewhere."

Conclusions

- All drugs have beneficial and harmful effects. The mission of the various members of the team is to ensure that medical products are safe and effective for their intended uses and support timely access to innovative therapies that improve patient outcomes.
- Efforts of the medical teams have focused on enhancing benefit–risk assessment to improve transparency and consistency in the regulatory decision-making and to improve communication with external stakeholders.
- Insurance payers routinely use regulatory seal of approval as a key consideration in reimbursement decisions.
- Professional societies and individual clinicians rely on complete evaluation of benefit–risk by unbiased experts as critical to promoting effective therapies and protecting the public from harm.

Conclusions, contd.

- The benefit–risk balance is a complex problem of balancing multiple efficacy and safety outcomes, their probability and uncertainty, using value judgments.
- Considering that there are many approaches available for conducting benefit–risk assessment, in general, the regulatory agencies favor a descriptive or qualitative approach as highlighted by their operational philosophy that “benefit–risk assessment is essentially a qualitative science grounded in quantitative data and dependent on judgment.”
- 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.

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Next Meeting

Sunday July 7th 4PM