THE ANNALS OF "DUNĂREA DE JOS" UNIVERSITY OF GALATI
FASCICLE III, 2016, VOL. 39, NO. 2, ISSN 2344-4738, ISSN-L 1221-454X
ELECTROTECHNICS, ELECTRONICS, AUTOMATIC CONTROL, INFORMATICS

A PERSPECTIVE ON RISK-BENEFIT ASSESSMENT OF FOODS AND DRUGS

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Abstract: Risk-benefit assessment (RBA) is a relatively new discipline that integrates scientific knowledge on nutrition, toxicology and microbiology with human epidemiology, using common health metrics. Its possible applications in food safety or drug recommendation (How do we judge a food ingredient to be worth/safe to use? How do we choose among different medications for a given condition? etc.) confer it an important role in modern society. The article below aims at offering a short perspective on what is currently available for use, as well as on the specificities of the tackled problems, and also some new ideas to further improve the frameworks.

Keywords: Risk-benefit assessment, ontology, fuzzy expert systems, hierarchical systems, weighted argumentation framework.

1. STATE OF THE ART

In the US, the regulatory authority **–FDA (Food and Drug Authority) -** has developed a structure of a benefit-risk framework for both foods and medications, that groups the key decision factors into 5 categories (***2013):

• **Analysis of Condition** and **Current Treatment Options** provide a summary and assessment of the severity of the condition that the product is intended to treat and other therapies available for its treatment (this provides useful information for weighing the benefits and risks of the drug being reviewed)

• **Benefit** and **Risk** provide assessment of the existent evidence concerning the drug:

Benefit: the results of the clinical trials and the clinical meaning of primary and secondary endpoints, as well as appropriate analyses of sub-populations (different categories of people that might respond differently to the drug, and could, in response, have different degrees/types of benefits).

Risk: the adequacy of the safety database, the severity and reversibility of adverse events, and the potential for sub-optimal management in the post-market setting that may be of concern.

In assessing benefit and risk, consideration is also given to other factors that may be relevant for a particular drug review, including non-clinical pharmacology and toxicology data; clinical pharmacology (e.g., mechanism of action, pharmaco-dynamics, and pharmaco-kinetics); chemistry, manufacturing, and controls (CMC); and clinical microbiology.

• **Risk Management** –describes the possibilities to reduce the risk, or the ways to ensure that the drug is directed to those patients for whom the risk is considered acceptable (if the benefits for the (sub-) population outweigh the risks).

Both knowledge regarding the drug and that regarding the disease might contain Evidences (facts that are certainly true), and Uncertainties -reflecting our incomplete knowledge-and can be therefore updated as our knowledge develops with every new evidence acquired. Also, each decision factor has associated some Conclusions and Reasons, that help the benefit-risk assessment and offer an explanation for the final decision (the idea arising is that they might be translated into a rule-base for a specific medication).

In Europe, **EFSA (European Food Safety Authority)** is interested in the development of standard risk-benefit assessment methods of foods, and has conducted a few projects (QALIBRA, BRAFO) that developed methods and modeling frameworks [http:// www.efsa.europa.eu/ sites/ default/files/corporate_publications/files/strategy2020.pdf]. In QALIBRA, a practical approach is used, - the "directly attributable health loss" method, which considers the health consequences of conditions starting in just a single (average) year and (unfortunately) ignores interactions.

The QALIBRA software integrates adverse and beneficial health effects using DALYs or QALYs (Quality-Adjusted Life Years). These two measures are related but have opposite meanings: DALYs represent the number of healthy life years lost, whereas QALYs represent the number of healthy life years remaining (as defined by Institute for Health Metrics and Evaluation in Global Burden of Disease Project [http://www.healthdata.org/gbd]). The calculation for DALYs is:

$$DALYs = YLD \times W + YLL$$

(where: YLD is years lived with a disease, W is a weight representing the severity of that disease on a scale where 0 = no effect and 1 = death, and YLL is the years of life lost due to early death from the disease).

Assessing overall health impact requires estimates of intake of relevant adverse and beneficial foods or substances and of the corresponding dose-response relationships, (as in a normal risk or benefit assessment), and information on the severity of effects which can be represented by DALY weights. Also required is the age of onset, duration, and probability of recovery or death associated with each disease (available from national health statistics).

One remaining challenge, after the mentioned projects, is to "gather, develop and harmonize approaches for risk-benefit problem-formulation and –solving".

EFSA recommends a stepwise approach for the risk-benefit assessment, i.e. [www.**efsa**.europa.eu/ en/ **efsa**journal/pub/1673]:

1. **initial assessment**, addressing the question whether the health risks clearly outweigh the health benefits or vice versa,

2. **refined assessment**, aiming at providing semi-quantitative or quantitative estimates of risks and benefits at relevant exposure by using common metrics, and

3. **comparison of risks and benefits** using a composite metric such as DALYs or QALYs to express the outcome of the risk-benefit assessment as a single net health impact value.

The outcome of each step of the assessment should also include a narrative of the strengths and weaknesses of the Evidence base and its associated Uncertainties (just like the FDA approach).

So, although sustained efforts were made worldwide to address these issues, there is still much to be done. We do not have yet a feasible, unified, well-understood and widely applicable framework. Most interactions are purposefully omitted for the sake of simplicity and the approaches are sometimes informal and improvisational.

2. THE DRUG RECOMMENDATION PROBLEM: A HIERARCHICAL FRAMEWORK

The problem deserves the effort of building a specific ontology around it. In fact, two different ontologies are more appropriate because although food risk-benefit assessment is strongly related to drugs risk-benefit ratio, there still are some notable differences.

As compared to foods, medications have a quicker and stronger effect, that can be observed within minutes/hours/ days from the intake (on both the positive and the negative sides). Moreover, their composition is completely known and purposefully constructed, derived from known physiological effects (the so-called "mechanism of action"). So, compared to foods, drugs are *more amenable to expert rules modeling.* Side effects occur because the human organism is a highly complex, poorly understood hierarchic system, and the whole is much more than merely the sum of its parts. Therefore, it is difficult to weigh the risk(s) and the benefit(s) of a certain medication (benefit-risk ratio).

Most often, things are (and should be) weighed within a certain context, i.e, for a given particular individual- so, the risk-benefit ratio is to be judged differently, according to each and every specific case (see also the "sub-populations" of the FDA approach). Yet, some general features are to be accounted for each patient. According to (Edwards R.,1996), a "principles of three" is used for merit assessment, such that **seriousness**, **duration** and **incidence** are computed for both risks (adverse effects), and the benefits of a medication.

For instance, the seriousness of a side effect could take 3 qualitative values: fatal, disabling and inconvenient (or, simply, high, medium and low), while the benefits could be expressed in terms of "level of improvement", that can also be high, medium, low. For instance, if the level of disability for a disease is judged as 10% by a healthcare practitioner, and a medication improves the condition of the patient with 10%, then we have a level of improvement of 100%, while if the disability is 80% and the cure of 10%, then the level of improvement is only (100/8)%. Always the side effects and the levels of improvement should be judged contextually, because they depend on many individual factors (for example, an antibiotic is more risky for a person whose liver's function is impaired). This contextual feature could be generally modeled by fuzzy rules given by field experts.

The idea of decision support systems (DSS) and, particularly, knowledge based systems (KBS) in risk management is not new, as this domain "relies heavily on experience, subjectivity and human judgment, and the problems are poorly structured and can not be formulated at the desired level of precision due to the surrounding uncertainty" (Baloi D. 2003), as we have seen above .

We will subsequently give some ideas of weighing the risks versus the benefits in medicine. Our opinion is that every field of interest should be hierarchically structured in order to avoid unrealistic behavior. For instance, in medicine, we might have the hierarchy in Figure 1, and reasoning should be done within each priority level, while the operators between levels (if they are to be considered at all) should not be simply cumulative, as more minor advantages shouldn't sum-up to counter-balance a fatal side-effect. Therefore, expert fuzzy systems should model uncertain reasoning for each level of priority separately.
After computing risks and improvements a vectorial ordering relationship is needed for the final decision:

Definition. $(I_1,\dots I_n)<(A_1,\dots,A_n)$ (higher priority Improvements/ Adverse effects come first) iff $I_i=A_i, 1\le i\le k-1$ and $k\le n$ such that. $I_k<A_k$

I_j's and A_j's could be the sum of realization degrees of improvements/adverse effects at priority level j.

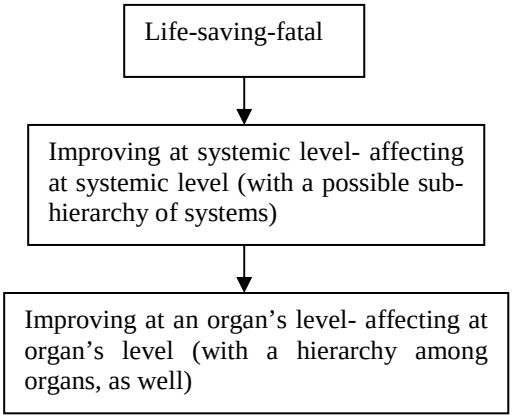

Fig.1. Side-effects/improvements should consider different layers of priority in medicine

An interesting, uninvestigated possibility within this field (from our knowledge), is to use weighted argument systems to solve conflicts that eventually occur between different layers (Dunne P., 2011).

3. FUZZY RULES IN DRUG RECOMMENDATION

Experts should compose two rule-bases for each priority level: one will produce some degrees of realization of specific risks, while the other will compute degrees of realization for the advantages specific to the level of priority considered (Boc K., 2012). Dempster-Shafer's evidential theory is not useful in building the set of rules because we do not deal with mutually exclusive hypotheses (Yen J. 1986).

Instead, we might get more relevant results by simply summing these degrees up into a score for the risks at this level (which we find more useful than simply taking the qualitative values of low, medium, high etc.)

Rule i: IF *Context i* THEN *Risk i*

(Context: Simultaneous medication, underlying condition- current diagnosis which may affect course of treatment, age etc.)

Rule j: IF *Condition j* THEN *Benefit j*

(Condition: NOT (exception j present) etc.)

Duration and incidence of improvements and adverse effects could be t-normed to weigh the rules.

4. CONCLUSIONS AND FUTURE WORK

Simple as it may seem, the above approach has one major challenge: the development of rules themselves, which is not always covered by existing knowledge, but has to be inferred from new evidence (especially when dealing with new medication, it is often obscure if a side effect arises from the medication alone, or from a specific interaction and a given –but unknown-context, or if it is to be attributed to completely independent causes). The existing reviews (Montgomery V. 2009; Baloi D. 2003) suggest nonparametric inference as a good choice to approach the problem, because it is particularly useful when there is very vague antecedent knowledge about the form of the distribution of a random quantity (Montgomery V. 2009). So, if statistical populations can be observed for each hypothesized rule antecedent, one can use Hill's assumption $A_{(n)}$ (Hill, 1968) to model tight probability intervals for the risks or improvements that hypothetically follow. Moreover, Spearman's rank correlation coefficient could be useful in suggesting the antecedent/consequent pairs to form the rules, starting from hypothetic explanations why the effect/improvement occurs /doesn't occur in some particular individuals.

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