

Objectives

Sheiner and Melmon defined the “Utility” of therapy as “Benefit - Harm” [1]. When Benefit and Harm are dichotomized to “absent” and “present”, best interpreted as random, and associated with unity costs, Utility becomes the probability of Benefit minus the probability of Harm.

The “true” costs of benefit and harm are hard to specify objectively, and the difference of probabilities (with unity costs) is hard to interpret, because it itself is not a probability.

Roozekrans *et al.* defined Utility as the probability of “Benefit And No Harm” [2]. Benefit and Harm are dichotomized continuous variables, with thresholds that need careful selection. The Utility becomes a function of - in addition to for example effect-site concentration - two thresholds, effectively decreasing its utility.

The objectives of the present study were:

- To reduce the dimensionality of the Utility Function (UF) by finding a way to handle the selection of the thresholds for dichotomization.
- To compare the characteristics of the original, Roozekrans', and an alternative specification of the Utility Function.

Methods

Instead of dichotomization, trichotomization was applied, by using the fuzzy logic [3] terms “low”, “moderate”, and “substantial”, where the thresholds for membership still need to be chosen, but are more informative than just “absent” and “present”.

With two Desirability Functions [4], each associated with a fuzzy set of three members, nine fuzzy rules were defined to have output Utility values of “very low”, “low”, “no”, “high” and “very high”.

Benefit \ Harm	Low	Moderate	Substantial
Low	No	Low	Very Low
Moderate	High	No	Low
Substantial	Very High	High	No

Benefit and Harm were simulated using sigmoid functions with lognormal distributions for the pharmacodynamic parameters C_{100} and γ , where C_{100} is the effect-site concentration giving a 100% increase of effect relative to (an arbitrary) baseline, and γ a shape parameter. Thresholds for “moderate” and “substantial” were set to 25% and 50%; see Figure 1.

From $N = 25000$ simulated values, their membership to the fuzzy sets were calculated by the number of times the values were within the threshold ranges (0, 25%, 50%, and infinity) divided by N .

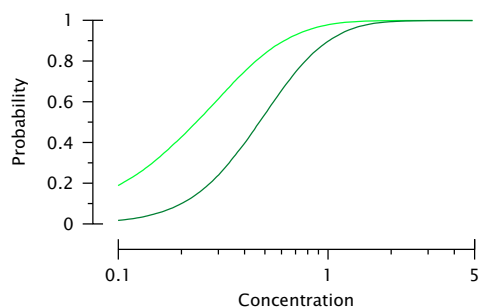


Figure 1: Standard sigmoids used to construct Desirability Functions ($C_{100} = 1$, $\omega^2 = 0.25$, $\gamma = 1$).

Results

- The classical Utility Function may be zero, negative, or positive, depending on which thresholds are chosen; see Figure 2.

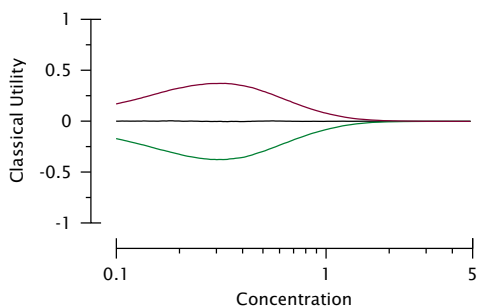


Figure 2: Classical Utility Functions, $P\{\text{Benefit}\} - P\{\text{Harm}\}$, for the different thresholds.

- The effects of changing the thresholds on the Utility Functions defined by Roozekrans *et al.* [2], can be visualized for one threshold at a time; see Figure 3. To the left of the black line, $P\{\text{Harm}\} < 50\%$; to the right of the black line, $P\{\text{Harm}\} \geq 50\%$.

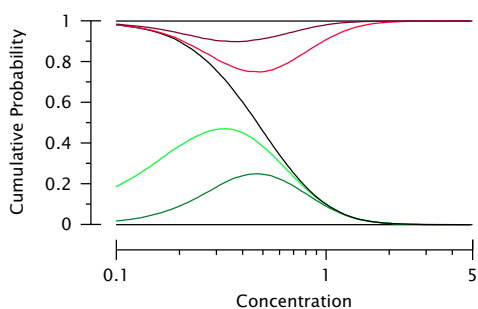


Figure 3: $P\{\text{Benefit And No Harm}\}$ (green lines) and $P\{\text{Harm And No Benefit}\}$ (red lines) for two thresholds for Benefit, but only one for Harm.

- The five Fuzzy Utility Functions are shown in a cumulative way as areas in Figure 4. Even though both thresholds are taken into account for both Benefit and Harm, the figure contains one line less than Figure 3.

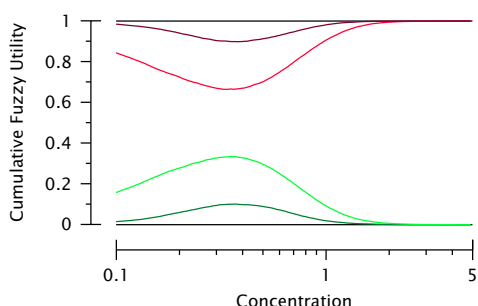


Figure 4: Area below dark green line: very high utility; below bright green: high utility; below bright red: no utility; above bright red: low utility; above dark red: very low utility.

The effect of a difference between the parameters for Benefit and Harm are the most important for decision making about competing therapies. Findings based on the present simulations include the following.

- With thresholds $< 100\%$, an increase in the γ for Benefit is likely to give lower values for high utility, and higher values for low utility; see Figure 5.

Results (continued)

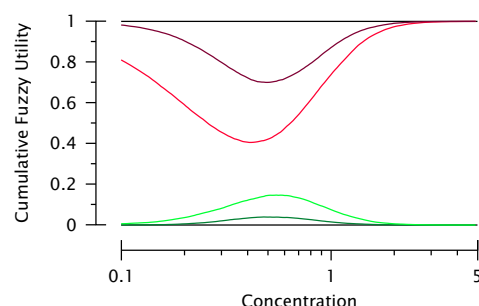


Figure 5: Utility Functions for the condition where the steepness for Benefit ($\gamma = 2.5$) is higher than for Harm ($\gamma = 1$).

- A higher (population) uncertainty of the value of C_{100} for Harm moves the UF downward for high utility, and upward for low utility; see Figure 6.

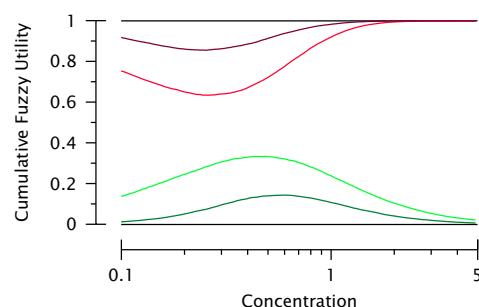


Figure 6: Utility Functions for the condition where the interindividual variability for Harm ($\omega^2 = 1.25$) is higher than for Benefit ($\omega^2 = 0.25$).

Conclusions

- While the term “Fuzzy Utility Function” might be proposed for the ones studied here, it might actually give a more crisp interpretation than one with just two thresholds for dichotomization, where it provokes discussion on how these should be chosen. However, this depends on how “easy” it is to define “moderate” and “substantial” Benefit and Harm.

- As Renard *et al.* note [4], the classical UF can have the value of zero for the entire dose or concentration range. In that case, there can indeed still be a value for the effect-site concentration that gives the highest value of “high” or “very high” utility, even if these are matched by simultaneous highest values of “low” and “very low” utility.

- Instead of one classical UF, the present approach gives about four UFs to consider when comparing two drugs. It could be possible that one drug gives higher values for “very high” utility, but even much higher values for “very low” utility; it depends on the application how these should be interpreted.

References

- [1] L B Sheiner and K L Melmon. The utility function of antihypertensive therapy. *Ann N Y Acad Sci*, 304:112–27, 1978.
- [2] M Roozekrans, R van der Schrier, I Aarts, E Sarton, M van Velzen, M Nies-ters, A Dahan, and E Olofsen. Benefit versus severe side effects of opioid analgesia: novel utility functions of probability of analgesia and respiratory depression. *Anesthesiology*, 128:932–42, 2018.
- [3] C A Naranjo, K E Bremner, M Bazon, and I B Turksen. Using fuzzy logic to predict response to citalopram in alcohol dependence. *Clin Pharmacol Ther*, 62:209–24, 1997.
- [4] D Renard, K Wu, R Wada, and G Flesch. Using desirability indices for decision making in drug development. *PAGE 18 (2009) Abstr 1506* [www.page-meeting.org/?abstract=1506].