The Kilim plot: a tool for visualizing network meta-analysis results for multiple outcomes

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Background

- **Network meta-analysis** (NMA) can be used to compare multiple treatments for the same disease. A range of outcomes is usually of interest.
- It is difficult to efficiently summarize results from NMAs on **multiple outcomes**, especially when the number of treatments and/or outcomes is large.
- NMAs often provide results in terms of **relative effect measures** that can be difficult to apply in **every-day clinical practice**, such as the odds ratios.

Aims

- Our predefined goals when developing the **Kilim plot** were the following:

*(1) to provide a method for visualizing the evidence from **multiple outcomes NMAs.***

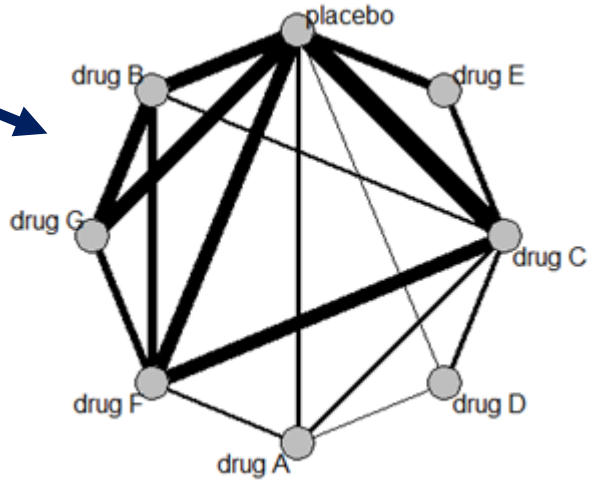
*(2) to present results in terms of **absolute**, rather than relative effects.*

*(3) to illustrate graphically the evidence with respect to **clinically important values.***

Clinical example: side effects of antidepressants

*We would have **nine** graphs since we have nine different side effects*

Network graph for nausea



- We used 297 RCTs on **antidepressants** for the **acute treatment of depression**.
- The studies compared **seven antidepressants and placebo** with respect to **nine different side effects** (all binary outcomes).
- Drug names have been **anonymized**.
- Three of the outcomes were **serious side effects**, i.e. *suicidal ideation, aggression, and accidental overdose*.
- Six outcomes corresponded to **frequent side effects**, i.e. *nausea, headache, dry mouth, insomnia, sexual dysfunction, and diarrhoea*.

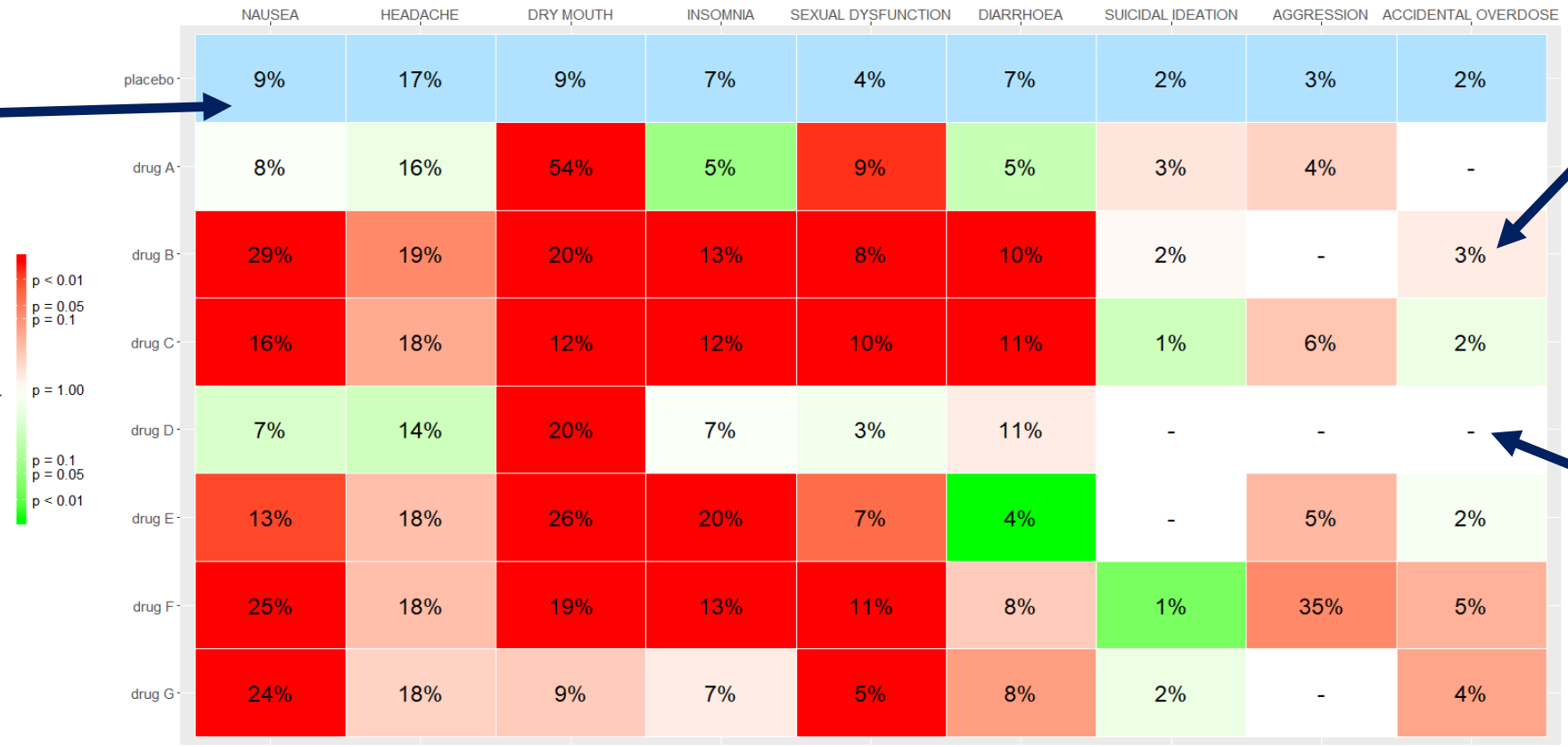
Drawing the Kilim plot

1. **Perform NMA** for all outcomes. This can be either a frequentist or a Bayesian NMA, using any NMA model.
2. **Perform a meta-analysis of the event rate** of the reference arms (or use external information) to obtain an estimate of the absolute event rate for each outcome, for the reference intervention.
3. **Combine the relative effects** from the first step and the **reference treatment event rate** from the second step in order to estimate the **absolute event rates for all treatments** in the network.
4. **Calculate Z-scores** using the estimated effect sizes and standard errors obtained from the NMAs of step one. For treatment X and outcome S, a Z-score equals to $Z_X^{(S)} = logOR_X^{(S)} / SE(logOR_X^{(S)})$
5. Use these information obtained (i.e. **Z-scores and absolute event rates**) to create the **Kilim plot**!

The Kilim plot

- We assume a negative (positive) Z-score is associated with a decrease (increase) in risk of side effects when using an active treatment as compared to placebo.
- **Green cells** denote a reduction in risk, **red cells** denote an increase in risk of a side effect

Estimates of absolute event rates are shown in the cells



When confidence intervals of relative effects vs. placebo are very wide the corresponding colors tends to white

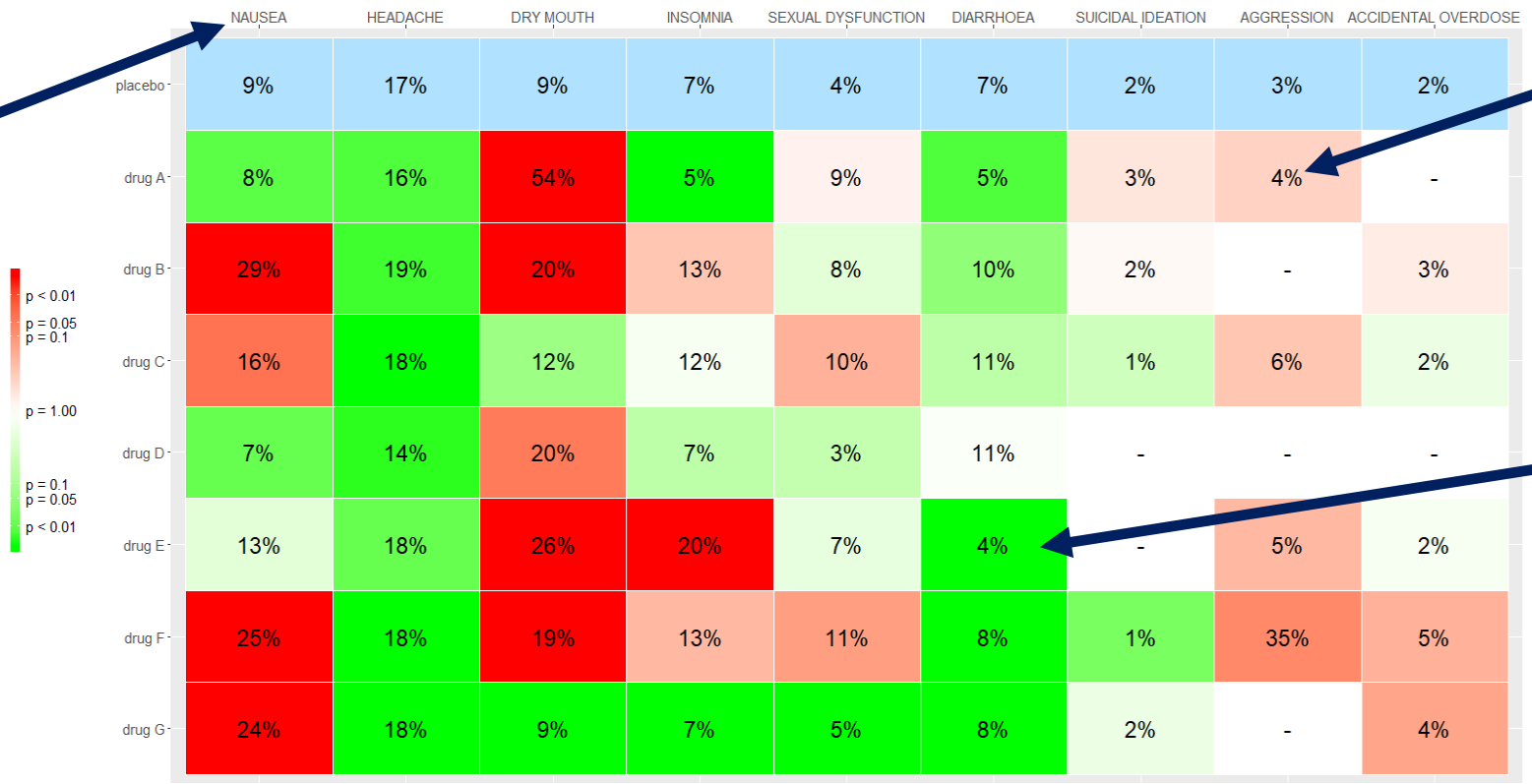
Coloring scheme is shown in terms of p-values, as calculated from Z-scores for relative effects vs. placebo

When a treatment is not included in the network the cell is empty

Incorporating clinically important values

- Assume a **clinically important value** $CIV_{RD}^{(S)}$ for the increase in risk compared to placebo, for outcome S. E.g. we deem that an increase of up to 5% in the risk of minor side effect S is acceptable.
- We use $CIV_{RD}^{(S)}$ to calculate $CIV_{OR}^{(S)}$, i.e. the clinically important value in the odds-ratio scale.
- We calculate $Z_X^{(S)} = (logOR_X^{(S)} - CIV_{OR}^{(S)})/SE(logOR_X^{(S)})$, where X denotes a treatment, and use this to color the cells.

For non-serious outcomes (ie, all outcomes except suicidal ideation, aggression, accidental overdose) $CIV_{RD}^{(S)}$ is set to a risk increase of 5%. For serious outcomes we set $CIV_{RD}^{(S)}$=0.



Estimated event rates remain the same, only colours change in cells according to the choice for $CIV_{RD}^{(S)}$.

*Dark green cells for non-serious outcomes indicate **strong statistical evidence** that the corresponding drug leads to an increase of event rate **less than 5%** as compared to placebo, for the corresponding outcome.*

Conclusion

- The **Kilim plot** can help in visualizing results from NMAs on multiple outcomes.
- It can be especially useful for **larger networks**, for the case of **many outcomes**, and when aiming to communicate NMA results with patients and/or clinicians, so as to facilitate **every-day clinical practice**.
- We illustrate the Kilim plot via an interactive web application (https://esm.ispm.unibe.ch/shinies/kilim/).
- Paper published in the Research Synthesis Methods Journal, https://doi.org/10.1002/jrsm.1428, R codes freely provided.

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