

# Testing Multiple Outcomes Across Mental Health Treatment Options: An Example Using Antidepressants

Tara Trujillo<sup>1</sup>, Rui Duan<sup>2</sup>, Jiayi Tong<sup>3</sup>, Yong Chen<sup>3</sup>, Joel Stoddard<sup>1</sup>

<sup>1</sup> Pediatric Mental Health Institute, Department of Psychiatry, School of Medicine, University of Colorado

<sup>2</sup> Department of Biostatistics, Harvard T.H. Chan School of Public Health

<sup>3</sup> Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania

## Background

Mental health providers balance the risks and benefits of treatment decisions by assessing prior evidence. For example, the risk of suicidality with antidepressant treatment for adolescent depression is justified as acceptable by considering the benefit, given the number needed to treat (NNT) of 9 for improvement in depression qualitatively outweighing the number needed to harm (NNH) of 59 for suicidality. This approach, however, becomes unwieldy with the consideration of more treatment options in different modalities, multiple effects, and outcomes. The informal aspect of the process often results in arbitrary decisions based on coarse criteria without a way to test for the superiority of a risk-benefit decision over another. *It is now possible to compare the strength of evidence for multiple treatments and outcomes formally.*

## Methods

### PALM analysis approach

- Patient-centered treatment ranking via Large-scale Multivariate network meta-analysis (Duan 2022) is a novel multivariate network meta-analysis that simultaneously assesses multiple outcomes.
- Determine a priori thresholds for acceptable risks at different benefit levels of a treatment option (personalized utility function).
- Rather than separately quantifying risks and benefits, multiple outcomes can be jointly considered through a weighted utility function. Jointly estimates the strength of evidence for both efficacy and harm to provide evidence-based guidance for patients and clinicians facing treatment decisions.
- Treatment ranking of more than two treatments using weighted SUCRA (surface under the cumulative ranking curve). The WSUCRA synthesizes multiple treatment effects into a single value which ranges from 0 to 1. The higher the value of WSUCRA indicates a better treatment based on the personalized utility function.

**Cipriani et al. 2018:** *Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis*

- Comparison of 21 antidepressants and a placebo
- Total of 522 RCTs comprising 116,477 adult patients
- The two outcomes were modeled separately; therefore, joint inference on a weighted function of both the treatment efficacy and the acceptability is not available.

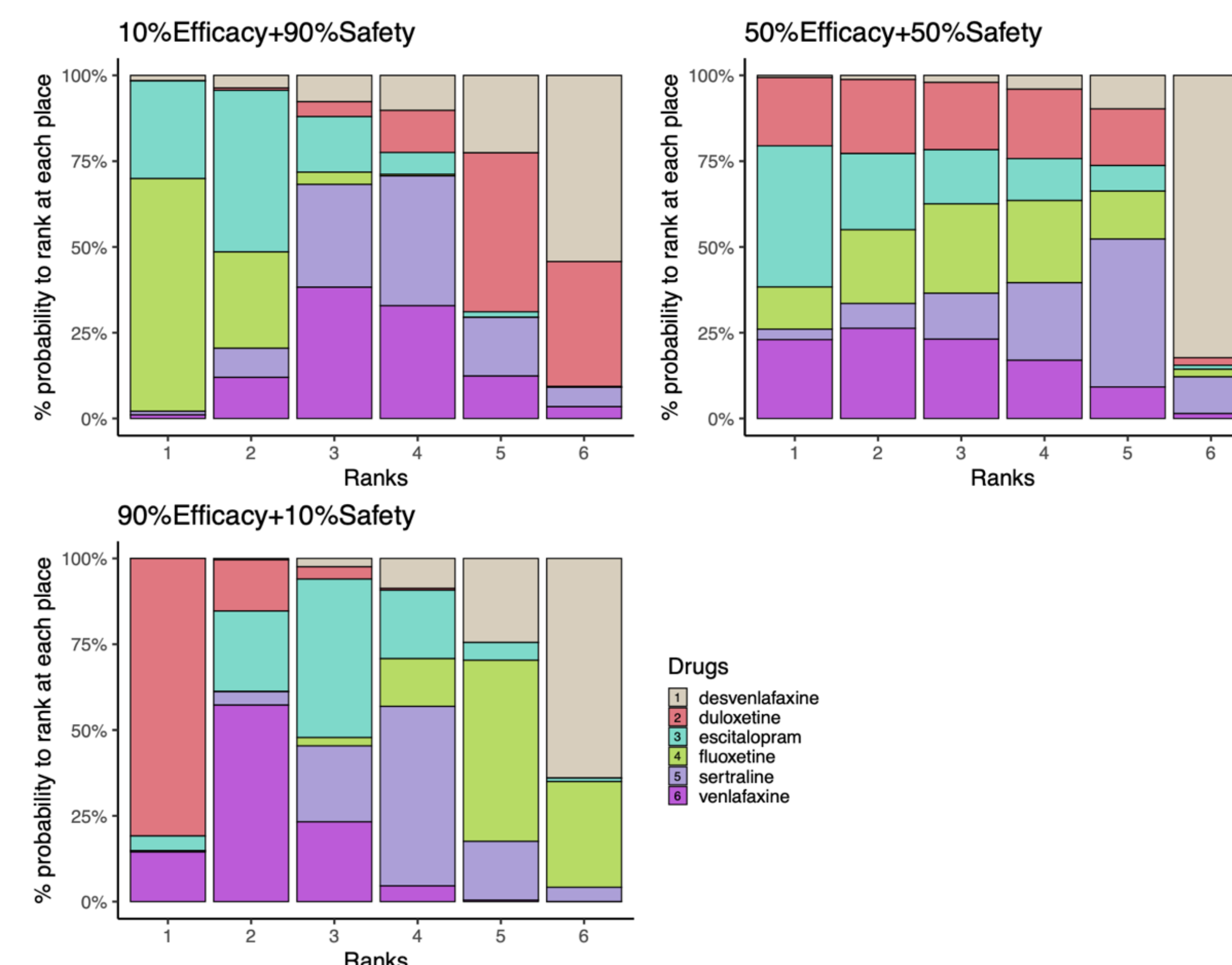
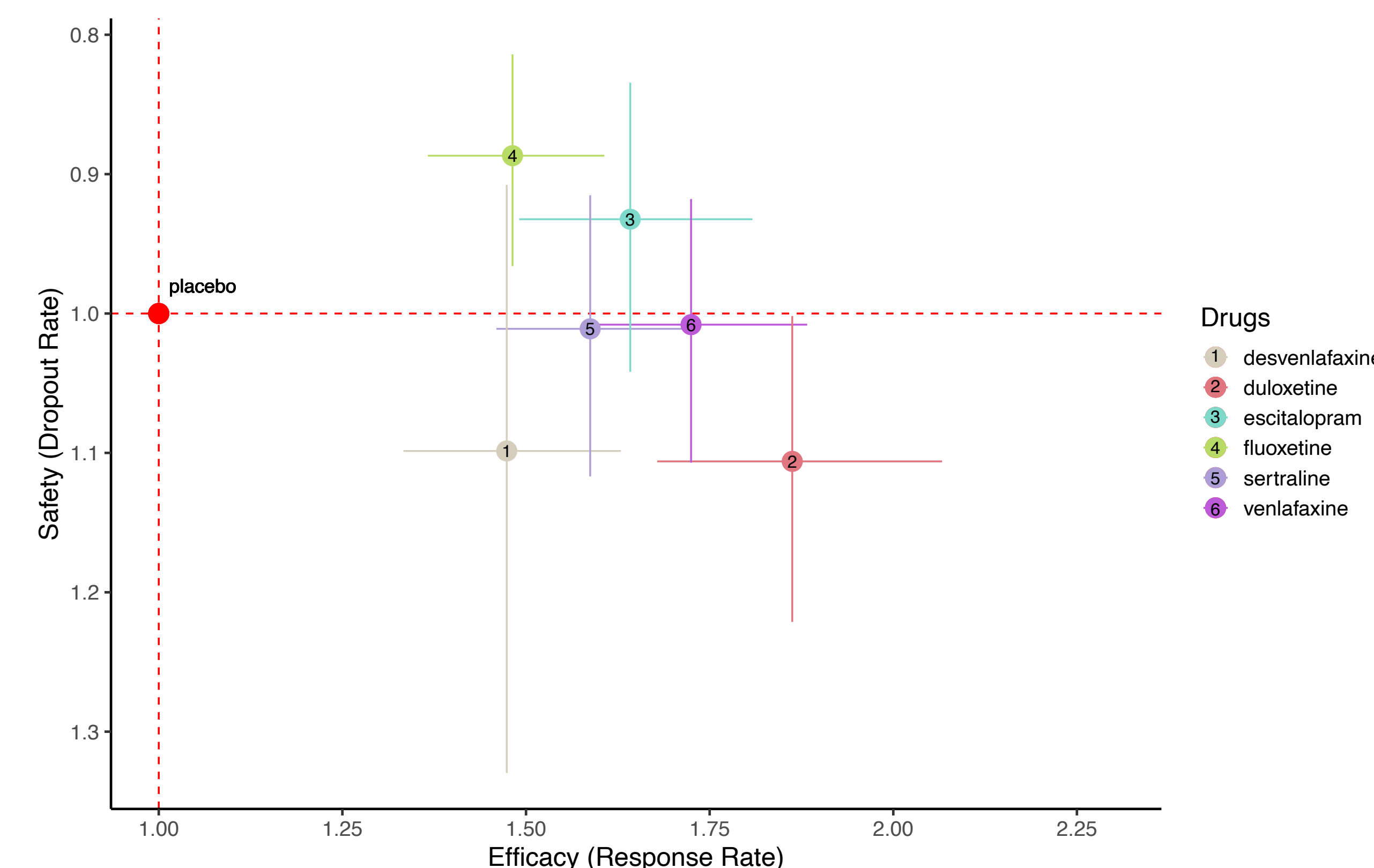
### PALM analysis applied to Cipriani et al. 2018

- Among the 21 drugs, selected 6 commonly used SSRIs and SNRIs to illustrate a common clinical concern of weighing their efficacy against their acceptability.
- To jointly consider the two outcomes, we define a combined outcome by assigning different weights to the two outcomes and calculating the weighted sum.

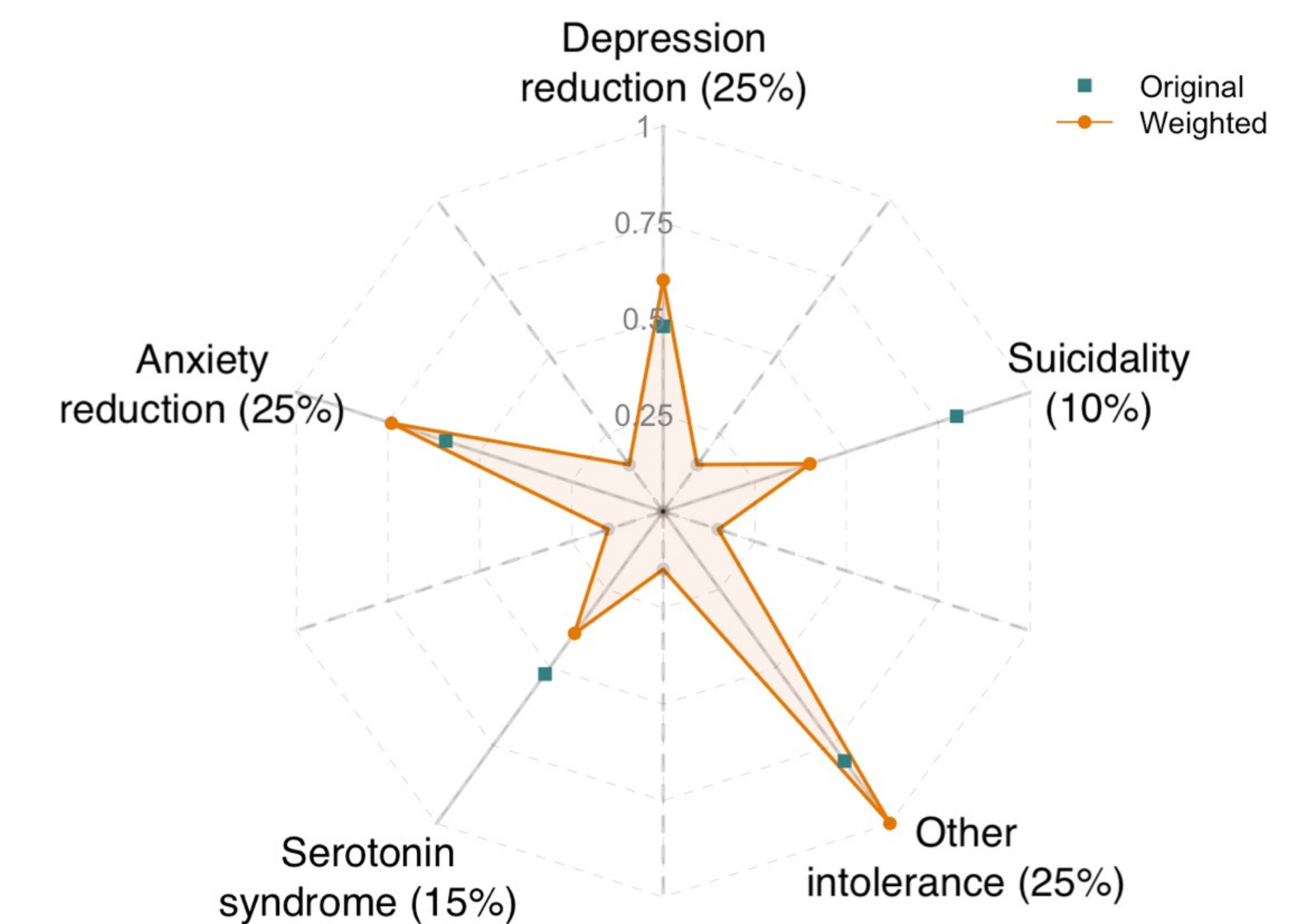
## Results

The scatter plot in Figure 1 shows the estimated odds ratios as well as the corresponding 95% confidence intervals for both the treatment efficacy and acceptability. Agents in the SSRI class had similar efficacy, clustering together in a narrow band of the efficacy scale with no significant difference. For drug acceptability, only fluoxetine is observed to be significantly better than placebo, meaning that only fluoxetine had fewer dropouts than the placebo group.

The bar charts in Figure 1 show the probability of each treatment ranking from the first place to the sixth place based on the combined outcome.



**Figure 1:** Scatter plot and rankings based on utility functions of selected antidepressants: Escitalopram, Sertraline, Fluoxetine, Duloxetine, Venlafaxine, Desvenlafaxine.



**Figure 2: Weighted origami plot—a novel visualization tool for multiple outcomes.** Hypothetical origami plot demonstrating 5 different outcomes for a single treatment. Each treatment gets its own star plot. Different metrics are assigned weights summing up to 100%. An overall score calculated as the weighted average score across five metrics is proportional to the area of the connected regions. The green squares show the original attribute scores if all outcomes were weighted equally. The vertices of the weighted star are the weighted scores. The length of the arms is based upon the calculated SUCRA value for the corresponding outcomes. Higher SUCRA values and therefore longer arms indicate a better treatment based on the corresponding outcomes.

## Discussion

Our PALM reanalysis of Cipriani et al. (2018) jointly tested two outcomes, but PALM also allows for many more. The power of this type of analysis is the ability to consider any number of outcomes and rank any number of treatments based on weighted utility functions including all these outcomes. The results of these can be clearly visualized and discussed by provider and patient, as demonstrated in the origami plots. Therefore, a major goal for practice guidelines may be to defining clear, widely acceptable utility functions for different mental health treatments to increase transparency in the treatment comparison. This will allow, for the first time, for personalized clinical decision-making when it comes to choosing mental health treatment. Next steps include utilizing this PALM approach to examine the efficacy and safety (specifically suicidality) in children and adolescents taking antidepressants for depressive and anxiety disorders.

## References

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