METHODOLOGICAL LIMITATIONS OF COMPARATIVE EFFECTIVENESS RESEARCH ON ANTIDEPRESSANTS: A SIMULATION STUDY

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Are we able to conclude on antidepressant efficacy for depression with the current methodology of RCT?

BACKGROUND

- Antidepressant's efficacy in depression is debated because their trials are criticized.
- Several pitfalls may limit the statistical power of antidepressant RCTs and their ability to conclude:
  - Sample heterogeneity due to poor reproducibility of DSM diagnosis
  - Sample heterogeneity in disease severity
  - Use of controversial outcomes
- We found no study analysing their simultaneous impact on the power of RCTs.

OBJECTIVES

- To study the impact of several design's element on the statistical power of RCT on antidepressant in depression

METHODS

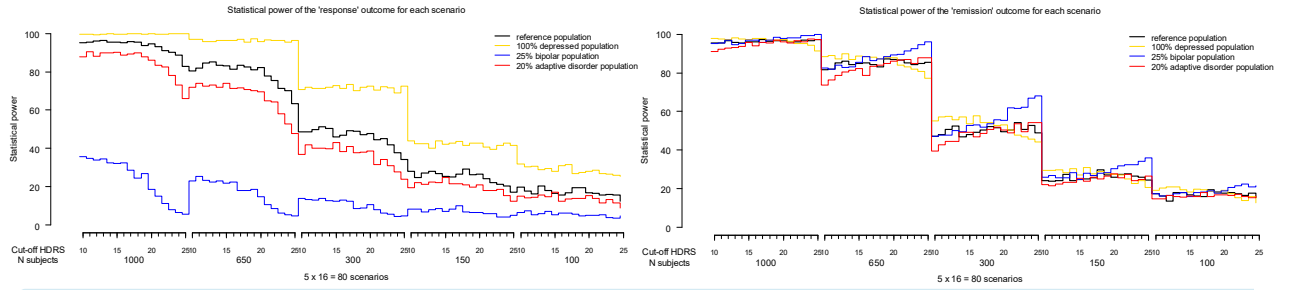
- Modelisation of one subject's response to the medication for each item of the Hamilton Depression Rating Scale (HDRS-one of the most used main outcome for trial on antidepressant in depression)
- The model takes into account:
  - Pre-treatment scores
  - Item quotation reproducibility
  - Response to placebo and natural variation of scores
  - Within-subject correlation
  - Between-subject variability
- Calibration of the model was done using literature data
- Simulation of 960 scenarios:
  - 7 different types of drug
  - 4 various case-mix of differential diagnoses in the sample:
  - 5 sample sizes
  - 3 types of outcome measures: response (HDRS<8), remission (HDRS score decrease by at least 50%) and continuous (t-test).
  - 15 different HDRS minimal scores for patient's inclusion

RESULTS

Sensitivity of statistical power to sample heterogeneity

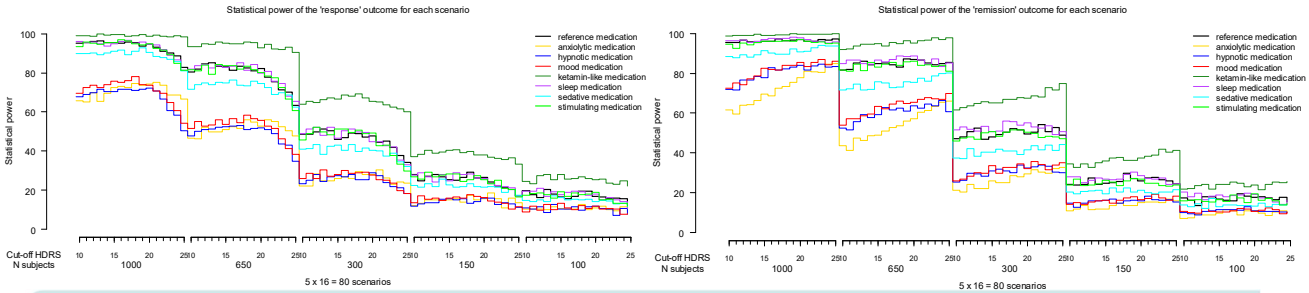
We simulated 4 samples:

1. In **black**: « Reference population » is composed by: 75% depression, 8% bipolar disorder, and a mix of adaptive disorder (AD), substance abuse disorder (SAD), post traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and schizophrenia.
2. In **yellow**: 100% depression
3. In **blue**: 55% depression, 25% bipolar disorder and a mix of GAD, SAD, AD, PTSD and schizophrenia
4. In **red**: 55% depression, 20% adaptive disorder and a mix of bipolar disorder, GAD, SAD, PTSD and schizophrenia



Response' outcome was highly dependent to sample heterogeneity whereas 'remission' outcome was not

Sensitivity of statistical power to the type of drug



- Sample sizes under 650 subjects yielded a power under 90% whatever the scenario
- HDRS score at inclusion has marginal impact on the statistical power
- Trials on drugs that only have an elective effect on few items (sleep, sedative, mood and stimulating medication) had lower power

DISCUSSION

- Sample size of most studies is too low due to methodological limitations such as heterogeneity and outcomes
- Lack of power leads to studies that are unable to provide adequate evidence
- Improvements in trial design of antidepressant medications should be made in order to limit waste in research

DISCLOSURE: THE AUTHORS REPORT NO CONFLICTS OF INTEREST FOR THIS WORK