Methodological limitations of comparative effectiveness research on antidepressants: a simulation study

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The Methodological Question Being Addressed:

Impact of the design of Randomized Controlled Trials on antidepressants in Major Depressive Disorder on their statistical power.

Introduction:

Randomized controlled trials (RCT) and their meta-analysis are the gold standard of Evidence Based Medicine for Clinical Effectiveness Research. Efficacy of selective serotonin reuptake inhibitor (SSRI) antidepressants is debated because of limits of their trials' design[1,2]: heterogeneity of included pathologies (not only major depressive disorder (MDD) but also bipolar depression (BD), generalized anxiety disorder (GAD), schizophrenia etc), use of poor reproducible DSM diagnosis, use of controversial main outcomes like Hamilton Depression Rating Scale (HDRS) measuring severity of the depressive disorder and low power. These pitfalls have been studied separately in the methodological literature and to our knowledge, no global modeling of the properties of the RCT on antidepressant medications has been proposed yet. Our hypothesis was to consider RCT as complex systems and to model them in order to study their behavior in terms of statistical power, using Monte-Carlo simulation.

Methods

Using an ordinal logistic regression, we modeled one subject's response to the medication for each HDRS item depending on the pre-treatment score, item's test/retest reproducibility, response under placebo, and specific effect of the medication. We used a random effect on the subjects to allow intersubjects variability. We modeled 7 medications according to their differential effects on each HDRS item with the same global effects as reported by SSRI in the literature. Calibration of the model was done using data from the literature. We simulated 960 scenarios to study the influence of heterogeneity of included patients' diagnosis (variate proportion of different diagnosis like MDD, BD, GAD, schizophrenia, PTSD, adaptive disorder, substance misuse); sample size (from 100 to 1000 subjects); threshold on initial 17-items HDRS score at inclusion time (from 10 to 25); type of outcome (HDRS<8, 50% lowering of initial HDRS score, or continuous criteria with a t student analysis) and different methods of statistical analysis (single analysis with ANCOVA, or multiple analysis with Holm or Hochberg correction or with a global testing procedure on the study power. Simulation and analysis were performed using R.

Results

A sample size under 650 patients yielded a power under 90% whatever the scenario. HDRS score at inclusion had a marginal impact on statistical power. Trials on medication that only have an elective effect on a few items had a lower power. Heterogeneity of the sample markedly impacted power and, using HDRS<8 as an outcome, was the most robust method against this loss of power. Separate analysis of groups of HDRS items with Holm or Hochberg correction for multiple testing yielded higher power.

Conclusion

Sample size of most studies is too low**;** use of outcomes based on HDRS may reduce power. Lack of power leads to studies that are unable to prove adequate evidence. Improvements in trial design of antidepressant medication should be made in order to limit wasted research**.**

Disclosures:

The authors report no conflicts of interest for this work

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