The IMPACT Study: A Randomized Placebo-Controlled Trial using an N-of-1 Design

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SUBMISSION DETAILS

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Methodological Issue Being Addressed This poster presents a novel study using n-of-1 design to test a short-acting drug, methylphenidate, in the treatment of post-traumatic stress disorder.

Introduction A randomized placebo-controlled N-of-1 trial design has several novel advantages. Each participant spends time on both active drug and placebo in random order under double-blind conditions, so that an estimated effect size and associated confidence interval can be calculated for each individual participant ('N-of-1'), while hypothesis testing is carried out across the entire cohort ('aggregated'). N-of-1 trial designs are effective in testing interventions whose effects are rapid in both onset and offset, in the treatment of conditions whose symptoms may fluctuate but are unlikely to fully remit in the absence of treatment, and in populations where response to treatment is likely to be heterogenous and/or the identification of response predictors is a scientific aim.

Methylphenidate's (MPH) rapid onset and offset of action (t 1/2 = 4 hours) makes it well suited to N-of-1 trial in the treatment of post-traumatic stress disorder (PTSD). One systematic review comparing 147 N-of-1 or crossover trials of MPH vs placebo for ADHD to 38 parallel group trials found consistent results across both methods, with no evidence of period or carryover effects (Krogh et al. BMJ Open, 2019:9(3), e026478).

Methods This poster presents the rationale and methods of an N-of-1 randomized placebo-controlled clinical trial of MPH in Veterans with PTSD and neurocognitive complaints. The study will assess the efficacy of MPH for reducing PTSD symptoms, improving subjective neurocognitive symptoms and objective neurocognitive functioning in Veterans with PTSD and neurocognitive complaints and characterize baseline predictors of treatment response to MPH compared to placebo. During the study, each participant (n=70) will move back and forth between periods of MPH and placebo. For each participant, the trial consists of 2 double-blind cycles , each cycle consisting of 2 periods: 4-weeks on MPH and 4-weeks on placebo in randomized order, each followed by a 1-week washout. The primary outcome is the self-report PTSD Checklist for DSM-5.

Assuming the highly conservative estimate that that 80% of randomized participants will complete the first cycle and that 60% of those who complete the first cycle will additionally complete the second cycle, N=70 randomized participants will detect a minimal standardized effect size of 0.3 with 80% power. This is a smaller effect size than was observed in the pilot study for any of the endpoints in Aim 1 (effect size for MPH on PTSD symptoms 0.88) or Aim 2 (effect size for MPH on subjective neurocognitive complaints 0.34). We are powered to detect minimal clinically meaningful effect sizes rather than the effect sizes identified in our pilot study.

All randomized participants will be included in the intent-to-treat analysis. There are two levels of analysis that are typically completed for aggregated N-of-1 trials. The first is to estimate the effectiveness of the active study drug for key outcome measures in each participant individually, by comparing active study drug vs placebo within a cycle and across cycles. To test the primary and secondary hypotheses, we will further aggregate these individual N-of-1 results to determine the population estimate of the effect. The primary outcome (PCL-5 scores) is the dependent variable, and with the individual and the study arm (MPH vs placebo) as the levels of the model. The subject will be treated as a random effect (both a random intercept and a random slope), while study arm will be treated as a fixed effect. The within subject residual variance will similarly be assumed to be drawn from a common distribution. Using hierarchical (multi-level) Bayesian methods using normal likelihood distributions, a posterior probability of the overall difference between the MPH cycles and the placebo cycles will be produced. We will also investigate interactions between treatment effect and treatment set, and between treatment effect and treatment order.

Results The trial will begin enrollment in the fall of 2023; thus, no results are available for this poster.

Conclusion The study is being funded by VA Clinical Sciences R&D and is currently being launched. Our discussion with colleagues at ISCTM will provide additional input to strengthen the design and implementation of our trial.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation
Lori *	Davis *	Tuscaloosa VA Medical Center
Rebecca	Hendrickson	Puget Sound VA Healthcare System
Murray	Stein	University of California at San Diego
Murray	Raskind	Puget Sound VA Healthcare System
Sonia	Jain	University of California at San Diego

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