Is it worth it to personalize the treatment of PTSD? - A variance-ratio meta-analysis and estimation of treatment effect heterogeneity in RCTs of PTSD

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Short title:

Treatment effect heterogeneity in PTSD

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Abstract

Several evidence-based treatments for posttraumatic stress disorder (PTSD) are recommended by international guidelines (e.g., APA, NICE). While their average effects are in general high, non-response rates indicate differential treatment effects. Here, we used a large database of RCTs on psychotherapy for PTSD to determine a reliable estimate of this heterogeneity in treatment effects by (1) applying Bayesian variance ratio meta-analysis, and (2) estimating the treatment effect heterogeneity (TEH). In total, 66 studies with a total of 8,803 patients were included in our study. TEH was found for all psychological treatments, with varying degrees of certainty, only slight differences between psychological treatments, and active control groups yielding a smaller variance ratio compared to waiting list control groups. Across all psychological treatment and control group types, the estimate for the intercept was 0.12, indicating a 12% higher variance of endpoint values in the intervention groups after controlling for the endpoint ratio. This study is the first to determine the extent of increase in treatment effects of psychological treatments for PTSD by personalization. The results indicate that there is sufficient heterogeneity in treatment effects across all psychological treatment and control groups, which in turn allow personalizing psychological treatments by using treatment selection approaches.

Keywords: personalized psychotherapy; posttraumatic stress disorder; PTSD; meta-analysis; treatment effect heterogeneity

Introduction

Research on the course of posttraumatic stress disorder (PTSD) showed that in 20-30% of all patients, posttraumatic symptoms are chronic (Chilcoat & Breslau, 1998; Frommberger et al., 2014; Kessler et al., 2005). Thus, rapid and effective treatments are urgently needed to avoid chronification of PTSD and its associated factors, such as comorbid mental disorders or physical illnesses (Brady et al., 2000; Felitti & Anda, 2010; Frommberger et al., 2014; Sareen, 2014; Sareen et al., 2007) and the increased risk of suicide (Sareen et al., 2007). On average, both meta-analyses of randomized-controlled trials (RCTs) (Bisson et al., 2013; Cusack et al., 2016; Lewis et al., 2020) and practice-based studies (Herzog et al., 2020) supported the efficacy and, respectively, effectiveness for psychological treatments of PTSD in different settings. However, non-response rates exceed 50% on at least some measures in many studies, and dropout rates considerably range from 0 to 54% (Bradley et al., 2005; Schottenbauer et al., 2008), with dropout rates being higher in real-world studies than in RCTs (Najavits, 2015). In other words, this heterogeneity of treatment effects (Varadhan et al., 2013) indicates that people respond differently to psychological treatments even if they show similar symptoms and are treated by the same therapist with similar methods (Kiesler, 1966), calling for methodological optimization efforts to improve treatment outcomes. To achieve this goal, personalizing treatments to the individual patient might be a promising approach (Chekroud et al., 2021), e.g., by following treatment selection procedures based on clinical prediction models (Cohen & DeRubeis, 2018). In this regard and analogous to personalized medicine (Simon & Perlis, 2010), personalized psychotherapy – among other objectives – strives to determine which individual patient characteristics predict the outcome of a particular psychological treatment with the aim of achieving a better match between the individual and the treatment received.

In recent years, personalizing psychological treatments has gained remarkable attention, resulting in the development of new conceptual and methodological innovations, most prominently: the personalized advantage index (PAI) (DeRubeis et al., 2014). The PAI aims to determine stable prescriptive variables for treatment outcomes that, in turn, help to select an optimal treatment for an individual patient (Cohen & DeRubeis, 2018). Statistically, the PAI uses pre-treatment available patient characteristics (e.g., sociodemographic and clinical variables) to differentially predict the outcome of two or more treatments. The PAI was successfully applied in studies investigating antidepressants vs. psychotherapy (DeRubeis et al., 2014), antidepressants v. placebo response (Webb et al., 2019), cognitive-behavioral therapy (CBT) vs. interpersonal therapy (IPT) for depression (Huibers et al., 2015; van Bronswijk et al., 2019), CBT vs. psychodynamic therapy (PDT) for mild to moderate adult depression (Cohen et al., 2019), and EMDR vs. trauma-focused CBT for PTSD (Deisenhofer et al., 2018). In the case of multiple equally effective treatments, the PAI yields the potential to facilitate treatment recommendations.

While the personalization of psychological treatments to the individual patient's needs is highly relevant, a recent review of existing empirical studies concludes that different personalization methods improve outcomes to some extent, likewise highlighting that many of these studies are underpowered or lack hold-out samples, therefore likely overestimating the effects (Lorenzo-Luaces et al., 2021). Therefore, the question remains as to how much the effect of psychotherapy can be increased by treatments particularly tailored to the individual patient. A major problem is that the extent of personalization is limited by the degree of treatment effect heterogeneity (TEH). Personalization procedures can only be applied successfully in the case that there is sufficient TEH. Therefore, the extent of TEH indicates the margin that can realistically be achieved by personalizing psychological treatments. Statistically, there are four sources of variation in outcomes in parallel-group RCTs (Senn, 2016), i.e., between-treatment variation,

between-patient variation, within-patient variation, and patient-by-treatment interaction. To estimate all these variance components, cross-over trials are needed. However, delayed treatment effects, spontaneous remission, and regression to the mean (Plöderl & Hengartner, 2019) limit the feasibility of cross-over trials in psychotherapy. Nevertheless, parallel-group RCTs provide information insofar as if the variance of outcomes in the treatment group is larger than in the control group, this indicates TEH. The most common approach to studying TEH is to compare the standard deviations of the intervention and control groups of RCTs by calculating an effect size statistic that measures the relative heterogeneity of outcomes: the variance ratio (VR). The VRs of individual clinical trials in turn can be combined in meta-analyses. Previously, VR meta-analyses were performed for other types of treatment. Regarding the psychopharmacological treatment for mental disorders, differences in individual treatment responses have already been evaluated for antipsychotics in the treatment of schizophrenia (Winkelbeiner et al., 2019) and antidepressants in the treatment of depression (Plöderl & Hengartner, 2019), both indicating no evidence for TEH. However, the first VR meta-analysis concerning TEH in psychological treatments for adult depression yielded promising findings with an outcome variance that is 9% larger in treatment groups compared to control groups (Kaiser et al., 2020). The evidence of TEH in psychological treatments for depression highlights that estimating the extent of TEH might be a promising avenue to researchers developing tailored approaches in psychotherapy and practitioners who apply them, as it allows to assess whether personalization of psychotherapy is at all useful and what effects a possible personalization of psychological treatments can achieve. Kaiser et al. (2020) argued for conducting studies estimating the TEH also for other types of mental disorders. Following this recommendation, the present article aims (1) to perform a VR meta-analysis, and (2) to determine TEH in RCTs of PTSD treatment.

Methods

Study selection

In this meta-analysis, studies were selected from three meta-analyses on the efficacy of psychological treatments for PTSD (Bisson et al., 2013; Cusack et al., 2016; Lewis et al., 2020). Based on the recommendations of the American Psychological Association (APA Clinical Practice Guideline for the Treatment of PTSD), we included the following treatments in the meta-analysis: cognitive-behavioral therapy with trauma focus (TF-CBT) or without trauma focus (CBT), cognitive processing therapy (CPT), cognitive therapy for PTSD (CT), prolonged exposure (PE), brief eclectic psychotherapy (BEP), eye-movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET). Means and standard deviations (SDs) of endpoint scores (post-treatment) were obtained directly from the included articles. We compared subgroups of studies based on the type of control group (waiting list, treatment as usual, minimal contact, and active treatment) and on the type of treatment. In total, 66 studies with a total of 8,803 patients were included in our analysis.

Data analyses

For the purpose of this meta-analysis, we conducted a Bayesian random-effects meta-regression. Following previous studies (Cortés et al., 2019; Kaiser et al., 2020; Plöderl & Hengartner, 2019; Volkmann et al., 2020; Winkelbeiner et al., 2019), we used the logarithmic variance ratio ($\ln VR$) as a proxy measure of treatment effect heterogeneity (TEH). The $\ln VR$ is obtained by dividing the variance of the endpoint score of the treatment group by that of the control group and taking the natural logarithm of the result. An $\ln VR$ that positively deviates from zero may be regarded as evidence of relevant TEH. As the $\ln VR$ measures the overall effect of an intervention on outcome variability, it could yield biased results because it is not corrected for a possible mean-variance relationship (Nakagawa et al., 2015). We controlled for this relationship

by including the logarithmic endpoint ratio ($\ln ER$) as a covariate, as first proposed by (Volkman et al., 2020). The $\ln ER$ is defined as the natural logarithm of the ratio of mean treatment group endpoint scores to mean control group endpoint scores. By controlling for the influence of $\ln ER$ on $\ln VR$, we can distinguish changes in endpoint variance associated with the treatment from those resulting from a mean-variance relationship. Study-level random intercepts were included to estimate between-study variance. Bayesian statistical models allow the specification of a priori estimates for statistical models ('priors'). It is recommended that these priors are based on findings from previous studies (van de Schoot et al., 2018). Therefore, we based the priors of our analyses on a previous meta-analysis on TEH of psychotherapy for depression (Kaiser et al., 2020). For the intercept, a normal prior with a mean of 0.09 and a standard deviation of 0.024 was specified. For the regression coefficient of $\ln ER$ on $\ln VR$, a normal prior was specified with a mean of 0.471 and a standard deviation of 0.06. For all parameter estimates, 95% credible intervals (CrIs) were calculated. They are to be interpreted in such a way that the estimated parameter lies within the specified value range with a certain probability (that is, in this case 95%), given the evidence, allowing a more accurate interpretation compared to traditional significance testing. All statistical analyses were conducted using the R statistical programming language (R Core Team, 2021). Bayesian meta-regression models were carried out using the *brms* package (Bürkner, 2017). The package *openxlsx* was used to read Microsoft Excel files (Schauberger et al., 2021). The package *dplyr* was used for data cleaning (Wickham et al., 2021).

Derivation of TEH

Since participants in parallel-group RCTs are randomized to one of two or more conditions, only one endpoint score per individual can be observed. Thus, after determining an estimate for the variance ratio of psychotherapy for PTSD, further computational steps are required. Following the analysis of the relationship between the variability ratio and TEH by

Volkman et al. (2020), we assume that the endpoint score of every individual is composed of the endpoint score under the control condition and an additional treatment effect if the individual receives the intervention. As Volkman et al. (2020) demonstrated, assumptions about counterfactual endpoint scores can be made based on the correlation between the observed and the counterfactual endpoint score. For example, if an individual's correlation between intervention and control endpoint score is -.50, this individual is likely to show a lower endpoint score in the intervention group and a higher endpoint score in the control group. Conversely, if the correlation is .50, the patient is likely to respond in a similar way to both interventions. By specifying a range of possible correlations, an estimate of TEH can be derived with the following formula:

$$SD_{tx} = SD_{ctr} \times [(\sqrt{e^{lnVR} + \rho^2}) - \rho]$$

Where SD_{tx} is the standard deviation of the treatment effect, SD_{ctr} is the standard deviation of the endpoint scores in the control group, VR is the logarithmic variance ratio, and ρ is the correlation between treatment and control group endpoint scores. Since the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995) is the most widely used outcome measure in psychotherapy outcome studies on PTSD, we will base our calculation of TEH on this scale.

Simulation-based estimation of TEH

To contextualize our results and illustrate the practical implications of our findings, we performed a simulation analysis based on our estimate of TEH. We simulated possible endpoint scores and calculated the probability of observing clinically relevant differences in treatment outcomes. The CAPS endpoint values were simulated by sampling from a normal distribution with the average observed endpoint scores as means and the standard deviation of the treatment effect calculated in the previous step. 1000 datasets with 100 endpoint scores each were simulated. All possible combinations of the 100 endpoint scores were formed and their

differences were calculated. Differences that exceeded the minimal clinically important difference (MCID) of the CAPS (10.4 points) (Stefanovics et al., 2018) were counted and averaged. For example, if 40% of the difference scores exceed the MCID, the likelihood that a randomly selected patient will respond differently to two randomly selected interventions is 40%.

Results

The results can be reproduced using the R code and data sheet available at <https://osf.io/nt3ke/>.

Variance ratio meta-analysis

A complete summary of the results by treatment type and control type is displayed in Table 1. TEH was found for all psychological treatments included in the analysis, with varying degrees of certainty. Across all psychological treatment and control group types, we found a VR of $\alpha = 0.12$ (95% CrI [0.08; 0.16]), indicating a 12% higher variance of endpoint values in the intervention groups after controlling for the endpoint ratio. Specifically, we found a positive VR for all psychological treatment types included in the analysis with only small variation in intercept estimates ranging from $\alpha = 0.09$ (CPT, CT, BEP and EMDR) to $\alpha = 0.11$ (PE, TF-CBT). As expected, VR was largest in studies with waiting list control groups ($\alpha = 0.13$) and smallest in active control groups ($\alpha = 0.07$).

- Insert Table 1 here -

As a sensitivity analysis, we re-ran the model including all studies with naïve priors. Cauchy distributions were specified as priors for all parameters except for between-study variance, for which a Half-Cauchy distribution with non-negative variance was chosen. As described in the table, this did not substantially change the point estimates, but led to considerably wider credible intervals.

Estimation of treatment effect heterogeneity (TEH)

Based on the formula of Volkmann et al. (2020), we derived the boundaries of TEH on the CAPS. We chose a range of values for ρ from -1 to 1 in steps of 0.2. The standard deviation of the endpoint scores in the control groups of studies using the CAPS was 19.62 and the variance ratio was 1.12. Table 2 summarizes the results of this calculation as well as the estimated probability of observing TEH in a randomly selected patient based on the simulation analysis. We estimated the standard deviation of the individual treatment effect on the CAPS to be 20.81.

- Insert Table 2 here -

Discussion

Personalized treatment approaches highlight the particular role of treatment selection to maximize treatment outcomes. In fact, a treatment selection that can reliably assign patients to the treatment that is most effective for them is likely to improve treatment outcomes (Cohen & DeRubeis, 2018). However, this promising way to optimize treatment outcomes is only possible if there is evidence for sufficient heterogeneity of treatment effects that in turn allow personalizing psychological treatments. To our knowledge, this study is the first to determine the extent of increase in treatment effects of psychotherapy for PTSD by personalization. In this article, we could show substantial heterogeneity in treatment effects across all psychological treatment and control group types, compared to similar studies for psychotherapy (Kaiser et al., 2020) and antidepressants (Volkmann et al., 2020) for depression or antipsychotics for schizophrenia (Winkelbeiner et al., 2019), indicating that outcomes in psychological treatments for PTSD differ. In addition, all psychological treatment types showed heterogeneity in treatment effects, contrary to some psychological treatment types for depression (Kaiser et al., 2020). However, the psychological treatment types did not noticeably differ between each other

in their heterogeneity of treatment effects suggesting that a general trauma focus seems essential to most psychological treatments. According to our expectations, we found an increase in heterogeneity compared to waiting list controls and a decrease compared to active controls, both indicating that the intensity of the psychological treatment relative to the control condition matters. In line, a recent study used a treatment selection method based on the personalized advantage index (PAI) to predict Tf-CBT and EMDR and found that 50% did not receive their model-predicted treatment and could have benefited from a treatment assignment based on the PAI (Deisenhofer et al., 2018).

Taken together, we believe that the TEH we obtained in this study can be considered as a realistic estimation of what can be expected from approaches that establish an optimal fit between patient and treatment, i.e., treatment selection approaches. It not only explains the high degree of non-response to psychological treatment, but also highlights the need for reliable treatment selection methods. By providing a benchmark for the effects that may be expected from precision mental health care methods in psychotherapy, our results suggest that matching patient-to-treatment approaches seems like a promising future research endeavor.

Limitations and future directions

When interpreting the results of our VR meta-analysis and TEH estimation, several limitations must be taken into account:

First, our VR meta-analysis, like others in the field (Kaiser et al., 2020; Volkmann et al., 2020), relied on trial-level summary statistics. Individual patient data would allow determining TEH more accurately by including important patient-level covariates in statistical analyses, most importantly baseline symptom severity. Future studies should therefore conduct individual patient data VR meta-analyses as they yield also several other advantages. For an overview of this field, we refer to specific literature (Riley et al., 2021). Second, the variability of our estimate of TEH

(as indicated by the SD of the intercept) was high and exceeded those of a similar study for depression (Kaiser et al., 2020), suggesting unexplained between-study variance. This finding might be traced back to differences in study designs (e.g., session frequency, exclusion and inclusion criteria, diagnostic criteria and comorbidities) across studies. Due to a lack of statistical power resulting from the limited number of studies, we were unable to control for these design aspects. The ‘true’ TEH might therefore be higher or lower than reported. Third, a waiting list served as a control group in most studies, making it more difficult to directly compare treatments against each other. While effortful, including direct comparisons between treatments in RCTs would facilitate the development of personalized treatment approaches, e.g., by using the PAI (DeRubeis et al., 2014). Fourth, since treatment types did not differ markedly between each other in their heterogeneity of treatment effects, future studies should examine specific ingredients of psychological treatments to investigate if there are different underlying mechanisms of change and possible component-level sources of TEH. For example, the role of dysfunctional expectations in PTSD was recently highlighted by empirical (Herzog, Barth, et al., 2021; Herzog, Kaiser, et al., 2021) and conceptual studies (Kube et al., 2020), suggesting that expectation violation might be involved as a mechanism across treatment modalities.

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Declaration of interest

The authors report that they have no conflict of interest.

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