Pre-registration Protocol:

Pharmacological augmentation of exposure-based psychotherapy treatment for posttraumatic stress disorder: A systematic review

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1. Introduction

1.1. Rationale

Trauma-focused cognitive behavioral therapy is the first line treatment for posttraumatic stress disorder (PTSD) (1). Its emphasis lies on emotional and cognitive processing of the individual traumatic event and the resulting memory (2). In trauma-focused therapies such as Prolonged Exposure (PE), patients are instructed to reactivate their traumatic experiences and moreover are confronted with trauma-related stimuli (2). Several studies indicated the efficacy of PE along with other trauma-focused psychotherapies to reduce PTSD symptoms (3). However, approximately 50% of the patients report residual symptoms after treatment (4). Hence, improvement of already well-established treatments is required. One possible improvement could be the additional application, i.e., augmentation of trauma-focused therapy, by pharmacological agents. Several of such studies have recently been conducted, the time is thus ripe for a systematic review of the evidence. The efficacy of pharmacologically augmented interventions targeting memory processes has not yet been evaluated in reviews and meta-analyses.

Underlying memory processes

There is clear evidence that memories can be altered through pharmacological or behavioral interventions, sometimes profoundly, when they are reactivated (5). Retrieving a memory destabilizes the memory trace which is then susceptible for disruption (5–7). In this labile state, new and correcting information can be added to the trauma memory which allows the proper processing of the trauma (5–7). Moreover, destabilized memory traces can be weakened or even lost (5–7). Two processes which are associated with memory retrieval and alteration are memory extinction and reconsolidation. Memory extinction is accomplished through repeated exposure to trauma stimuli and leads to the creation of a new memory which replaces and suppresses to original memory (6,8). After memory extinction the still existing original trauma memory might recover spontaneously or through renewal and reinstatement and return when stimuli are presented in a new context (6,8,9). In contrast, memory reconsolidation aims to destabilize and modify the original fear memory (6,9). Memory reconsolidation comprises restoring of an already consolidated memory which entered a

temporary labile state after retrieval (6,8,9). During this limited time window memory modifications can be achieved by the presentation of new and corrective information (6,8,9). Further, the reconsolidation of memories may be blocked by the use of pharmacological agents (6,8,9). Several studies in animal and human samples have demonstrated the potential of memory reconsolidation for memory modification (5–7).

Pharmacological augmentation of memory-based PTSD treatment

The neurobiological processes such as memory extinction and reconsolidation that take place after trauma activation can be specifically strengthened or weakened with the application pharmacological agents (12). This is exactly where various options for augmentation come into play (12). For instance, pharmacological augmentation may on the one hand be achieved by strengthening extinction learning through exposure to traumatic memories (12). On the other hand, pharmacological agents may be applied to block the reconsolidation of recently retrieved trauma memories (12). Results of previous animal studies have demonstrated that those memory and learning processes can be targeted pharmacologically (12). Thus, such approaches have been translated to studies in clinical human populations and preliminary findings of anxiety disorder suggest an efficacious optimization of exposure therapy. Pharmacological augmentation of psychological interventions has also been analyzed in PTSD samples (6). Although pharmacologically augmented interventions have been examined in previous reviews and meta-analyses, only a limited number focused on the combination of two memory interventions to treat PTSD symptoms. Meta-analyses examining similar topics to the present one are Walsh et al. (13) and Metcalf et al. (12). In their meta-analysis, Walsh et al. (13) analyzed studies using interventions for substance use disorder (n = 10) as well as for anxiety, phobic and trauma-related disorders (n = 8). The interventions used in the included studies targeted on memory reconsolidation interference and were psychological as well as pharmacological enhanced interventions. In the meta-analysis of Metcalf et al. (12) only studies combining different interventions were examined. The authors were interested in the efficacy of pharmacological and psychological treatment augmentation. For instance, they examined intervention effects of Prolonged Exposure augmented by pharmacological agents or vice versa. Nevertheless, both meta-analyses did not limit their investigation on memory interventions only. A qualitative review conducted by de Kleine et al. (14) analyzed pharmacological augmentation of exposure based treatments. Contrary to our systematic review, the authors did not use as restricted inclusion criteria such as randomized controlled studies only or a minimum number of participants per treatment arm. Moreover, their emphasis lied on identifying and

describing the proposed underlying mechanism of the pharmacological agents rather than examining the efficacy pharmacological augmented interventions. Hence, it would be intriguing to compare the efficacy of different attempts of pharmacological augmented interventions targeting memory extinction or reconsolidation and to state under which circumstances they may be efficacious.

1.2. Objectives

The aim of this review is to investigate effects of pharmacological agents targeting memory extinction ore reconsolidation and used in combination with at least one exposure-based PTSD treatment session.

RCTs fulfill the following criteria:

1) RCTs report effects of exposure-based PTSD treatment
2) Pharmacological agents are used shortly before or after an exposure-based session.
3) Pharmacological agents' proposed mechanism of actions targets memory extinction or reconsolidation processes.

Research questions

1. What pharmacological agents targeting memory extinction or reconsolidation of the traumatic memory have been used in the context of exposure therapy for PTSD?
   a) Which pharmacological agents were used?
   b) What was the dosage?
   c) What was the timing in the context of exposure sessions?
   d) What is the proposed working mechanism of the pharmacological agent?

2. Effects of pharmacological augmentation of exposure therapy?
   a) What was the length and type of the augmented exposure session?
   b) Which combinations were successful and which were not?

2. Methods

2.1 Inclusion criteria

Randomized controlled trials (RCT) will be included that used a combined psychological and pharmacological intervention both targeting memory reconsolidation or extinction. Acceptable psychological interventions are manualized treatments such as Prolonged Exposure as well as the use of brief trauma reminders and memory reactivation. Further, a placebo control group must be used as comparator and the study must include at least ten participants per treatment arm. Requirements concerning study participants are that all participants had a PTSD diagnosis and were at least 18 years old. Lastly, the primary outcome of the study must be PTSD overall symptoms. Pilot studies which meet all inclusion criteria will be included as well. All kinds of prevention will not be included. Furthermore, all trauma types and population subgroups will be accepted.

2.2 Information sources

Studies will be retrieved from literature databases. A systematic search for literature will be conducted as detailed in the following section. Further, reference lists of previously published systematic reviews and meta-analysis will be screened to complementary search for potential studies. Lastly, study authors will be contacted if relevant information should be missing.

2.3 Search strategy and study selection

A systematic literature search will be conducted for full articles on the databases PubMed, PsychInfo, PsychNdex, PTSDpubs, MEDLINE and Cochrane. The database will be updated every three months before publishing the systematic review.

The search strategy will be obtained from the preparation of the German S3 treatment guideline for PTSD (Schäfer et al., 2019), and will include the following key words: (PTSD OR posttraumatic stress disorder OR Posttraumatische Belastungsstörungen or PTBS) AND ((treatment trial OR randomized controlled trial) or (*indexed by a thesaurus term as a clinical trial*)). Inclusion criteria for the database are (1) the study is an RCT, (2) PTSD is the primary outcome, (3) participants are18 years and older, (4) the study is a peer-reviewed publication and (5) each treatment arm has at least 10 persons. A systematic screening through all studies as well as a specific search with related key words will be conducted by two independent persons. The relevant key words are *reconsolidation*, *extinction*, (*re-)activation*, *combined*,

augmented, enhanced and *assisted*. Afterwards, the full articles of the screened pre-selected studies will be assessed for their eligibility based on our inclusion criteria. For those studies, it will be assessed whether the pharmacological agents target memory extinction or reconsolidation as well as whether an exposure-based intervention was applied.

In addition, we will perform a systematic snowball search by screening reference lists from included primary studies and relevant review articles. Two researchers will independently screen articles and decide on eligibility of the study. In cases of disagreement between the researchers, a third researcher will decide on eligibility.

2.4 Data collection

For data collection, the following study characteristics will be extracted: publication year, sample size, gender, mean age, PTSD diagnosis, comorbidity, trauma type, study origin, study design, PTSD measures, measurement times, intervention type and procedure, number of sessions, medication dosage as well as group means, standard deviations, standard errors and confidence intervals of PTSD symptom scales. To assess potential differences between trauma types, it will be decided whether studies can be assigned to one trauma type based on their study sample. A study will be categorized to one trauma type when the majority (70%) of the participants had experienced that kind of trauma.

2.5 Outcomes

Primary outcome is PTSD overall symptom severity at post-treatment. For all studies, results from intention-to-treat (ITT) analyses are preferred. If no ITT analysis was conducted, results from per-protocol analyses will be used instead. For the PTSD outcome, only data measured on a continuous scale at post-treatment will be examined. If a study used self-report and clinician administered measures for PTSD outcome, both measures will be combined and averaged using the formula below to obtain a more informative outcome measurement. The same will be done when studies used several measures for self-reported or clinician administered PTSD symptoms. The different measures used within one treatment group will be treated as if they were two individual groups which will then be combined with the only exception that after combining, the sample size is still the same. Subscale scores will also be pooled using the same formula if a study reported only scores for the subscales of a measure but not a total score.

Formula for combining two outcome measures and / or two groups:

$$M_{combined} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$SD_{combined} = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

where N_i is the sample size M_i the mean and SD_i the standard deviation of each group included for the analysis at this measurement time

If a study has more than two intervention groups, we will decide whether the additional groups received an active intervention or whether it was a passive / non-trauma focused control group. In the case of an active intervention, the group will be excluded and only the remaining groups will be considered for the analyses. However, if the groups is classified as an additional control group (in accordance with the study inclusion criteria) with a non-trauma focused intervention or no intervention at all, the groups will be combined using the same formula shown above and a new sample size will be calculated (sum of both sample sizes). If scores are only available for one of the control groups at post-treatment (e.g. if one control group was a waitlist control group), they will be adopted.

2.6 Risk of bias

Risk of bias will be assessed with the Cochrane Risk of Bias Tool (15). We will assess the effect of a pharmacological agent relative to placebo will be assessed. Using the tool, the following five domains are assessed: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported result. The risk of bias can be rated as *low*, *some concerns* or *high risk*. For each domain, it will be rated if there is a low risk, some concerns or high risk of bias. The answer option *no information* may be used when the published paper does not provide enough information to fully answer the signaling question. When any of the domains within a study is rated *high risk* or more than two domains are rated *some concerns*, the study is regarded overall at high risk for any bias.

2.7 Data synthesis

In this systematic review, studies will be analyzed and described in a narrative way. Main characteristics such as study sample and setting, description and application of the intervention as well as findings of each study will be detailed. Furthermore, study quality and conductance will be appraised critically. Although no meta-analysis will be performed, effect sizes will be calculated and plotted in a forest plot for a better comparability of the different studies. All effect sizes will be calculated and estimated as Hedges' g (16). Hedges' g is a standardized mean difference statistic and can be used when the analyzed studies used different instruments for measuring the same outcome (15,17). Its interpretation is as follows: a magnitude of 0.2 stands for a small, 0.5 for a moderate and 0.8 for a large effect (18). Group means and standard deviations of PTSD symptom scales will be extracted for the calculation. If standard deviations are not reported, other values such as standard errors or confidence intervals will be used for its calculation. For the imputation of the standard deviation the following formulas were used:

Calculation with the standard error:

$$\mathrm{SD} = \mathrm{SE} \times \sqrt{N}$$

Calculation with the 95%-confidence interval:

$$\mathrm{SD} = \sqrt{N} \times (\text{upper limit} - \text{lower limit})/3.92$$

where *N* is the sample size, *SD* the standard deviation and *SE* the standard error of each group included for the analysis at this measurement time

2.8 Meta-bias

A possible meta-bias is a publication bias which could impact the interpretation of the results found in this review. Therefore, it is crucial to check for a publication bias. This will be done through inspection of a funnel plot and additionally an Egger's regression test (19) will be performed for a statistical assessment of a potential bias.

2.9 Confidence in cumulative evidence

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria will be used to assess the strength of the body of evidence.

References

1. Schäfer I, Ehring T, Knaevelsrud C, Maercker A, Michael T, Schellong J. Diagnostik und Behandlung der posttraumatischen Belastungsstörung. Psychotherapeut. 2020 Nov 1;65(6):521–32.
2. Foa EB, Hembree EA, Rothbaum BO. Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences: therapist guide. Oxford ; New York: Oxford University Press; 2007. 146 p. (Treatments that work).
3. Merz J, Schwarzer G, Gerger H. Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: A network meta-analysis. JAMA Psychiatry. 2019 Sep;76(9):904–13.
4. Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG. Response rates for CBT for anxiety disorders: Need for standardized criteria. Clin Psychol Rev. 2015 Dec;42:72–82.
5. Treanor M, Brown LA, Rissman J, Craske MG. Can Memories of Traumatic Experiences or Addiction Be Erased or Modified? A Critical Review of Research on the Disruption of Memory Reconsolidation and Its Applications. Perspect Psychol Sci. 2017 Mar 1;12(2):290–305.
6. Elsey JWB, Van Ast VA, Kindt M. Human memory reconsolidation: A guiding framework and critical review of the evidence. Psychol Bull. 2018 Aug;144(8):797–848.
7. Nader K, Schafe GE, Doux JEL. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 2000 Aug;406(6797):722–6.
8. van Marle H. PTSD as a memory disorder. Eur J Psychotraumatology. 2015 Dec;6(1):27633.
9. Brunet A, Saumier D, Liu A, Streiner DL, Tremblay J, Pitman RK. Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial. Am J Psychiatry. 2018 May 1;175(5):427–33.
10. Kredlow MA, Unger LD, Otto MW. Harnessing Reconsolidation to Weaken Fear and Appetitive Memories: A Meta-Analysis of Post-Retrieval Extinction Effects. Psychol Bull. 2016 Mar;142(3):314–36.
11. Litz BT, Salters-Pedneault K, Steenkamp MM, Hermos JA, Bryant RA, Otto MW, et al. A randomized placebo-controlled trial of d-cycloserine and exposure therapy for posttraumatic stress disorder. J Psychiatr Res. 2012 Sep;46(9):1184–90.

12. Metcalf O, Stone C, Hinton M, O'Donnell M, Hopwood M, McFarlane A, et al. Treatment augmentation for posttraumatic stress disorder: A systematic review. Clin Psychol Sci Pract. 2020;27(1):e12310.
13. Walsh KH, Das RK, Saladin ME, Kamboj SK. Modulation of naturalistic maladaptive memories using behavioural and pharmacological reconsolidation-interfering strategies: a systematic review and meta-analysis of clinical and 'sub-clinical' studies. Psychopharmacology (Berl). 2018 Sep;235(9):2507–27.
14. de Kleine RA, Rothbaum BO, van Minnen A. Pharmacological enhancement of exposure-based treatment in PTSD: a qualitative review. Eur J Psychotraumatology [Internet]. 2013 Oct 17 [cited 2020 Dec 22];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3800126/
15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 1st ed. Wiley; 2019 [cited 2020 Mar 23]. Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604
16. Hedges LV. Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. J Educ Stat. 1981;6(2):107.
17. Borenstein M, editor. Introduction to meta-analysis. Chichester, U.K: John Wiley & Sons; 2009. 421 p.
18. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Academic Press; 1977. 459 p.
19. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.