Supplementary Material

Effectiveness of an adjunctive psychotherapeutic intervention developed for enhancing the placebo-effect of antidepressants used within an inpatient-treatment program of major depression: a pragmatic parallel-group, randomized controlled trial

Benedikt Bernd Claus[1] , Norbert Scherbaum[2], Udo Bonnet[1,2]

[1]Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Evangelisches Krankenhaus Castrop-Rauxel, Academic Teaching Hospital of the University of Duisburg-Essen, D-44577 Castrop-Rauxel, Germany

[2]LVR-Hospital Essen, Department of Psychiatry and Psychotherapy, Faculty of Medicine, University of Duisburg-Essen, D-45147 Essen, Germany

Corresponding author: Udo Bonnet, Evangelisches Krankenhaus Castrop-Rauxel, Grutholzalle 21, 44577 Castrop- Rauxel, Germany, Email: udo.bonnet@uni-due.de

Materials and Methods

Trial design and treatment regimen

This single-center 4-week pre-post pragmatic-parallel-group randomized study was conducted from May to September of 2018 in the psychiatric ward of the Evangelisches Krankenhaus Castrop-Rauxel, Germany. It was in accordance with the revised declaration of Helsinki and was approved by the local ethic committee of the Medical Faculty of the University of Duisburg/Essen, Germany. Written informed consent was obtained from participating patients. The inpatient treatment-as-usual (TAU) of Major Depressive Disorder (MDD) consists of 3 physician visits per week, pharmacotherapy, multimodal psychotherapy, specialist´s therapies (occupational therapy, music therapy, and dance therapy), psychiatric nursing and social counseling. The frequency of the therapeutic sessions was not different from the estimated benchmark performance of other psychiatric wards in German general hospitals (GSG Consulting, unpublished data). The inpatient face-to-face psychotherapy was based upon multimodal individual and group-psychotherapy (cognitive-behavioral, psychodynamic and humanistic elements including psychoeducation). Within the first four days after admission, eligible inpatients were randomly allocated (see below) either to TAU (control group, CG) or to the experimental group (EG) being defined as described below (Figure 1). The study protocol and statistical analysis plan were preregistered at the Open Science Framework (OSF) prior to data acquisition. For raw data, figures and further analyses refer to the online supplementary at OSF (http://osf.io/j439n).

Participants and eligibility criteria

We included adult (18- to 65-year-old) inpatients who sought treatment of their unipolar MDD of moderate (F32.1, F33.1) or severe (F32.2, F33.2) intensity according to ICD-10, were familiar with the German language, were without a lifetime diagnosis of schizophrenia or bipolar disorder, were currently not psychotic or misusing alcohol or drugs, had a Mini-Mental-Status-Test above 24 points and gave their written informed consent for study-participation. They had to agree to the study-protocol including an initiation, switching or augmentation of a treatment with antidepressants (ADs), lithium or atypical antipsychotics. Excluded were patients who did not give back the baseline self-report questionnaire (post-randomization

exclusion). Furthermore, patients were excluded who attempted suicide, used alcohol or drugs for recreational purposes during the hospital treatment, became psychotic or confused for longer than a 24 hour-period or were transferred to another department (e.g. due to somatic complications) for longer than a 7-day-period. Drop-outs were defined as those patients who terminated the inpatient treatment prematurely (e.g. withdrew their consent to participate, lost-to-follow up or being excluded).

Experimental group (EG)

The EG received TAU plus four brief psychotherapeutic group sessions which were offered weekly and aimed to enhance the placebo-effect (PE^+) and to weaken the nocebo-effect (NE^-) of ADs (”PE^+/NE^--psychotherapy”). The PE^+/NE^--psychotherapy was manualized prior to data acquisition, was based upon the recommendations of Klinger and Flor (1) as well as Sliwinski and Elkins (2) and was comprised of four 30-minutes-lasting group sessions.

The first session introduced the most common hypotheses of major depression. We explained the role of ADs to strengthen the synaptic activity of brain monoamines, neuroplasticity, resilience and hippocampal neurogenesis in order to improve major depression and anxiety. The patients were taught that the efficacy of AD in MDD-treatment corresponds approximately with a decrease of 10 points (3) in the Hamilton rating scale for depression. The latency of response to ADs was told to be usually 2 to 6 weeks. We mentioned that a favorable response to ADs does not occur in all cases and that it cannot be predicted with any certainty, who does respond and who does not respond to an AD. Potential adverse effects of AD were explained to have the power to induce negative expectations and, thereby, an augmentation of the nocebo-effect. The sense of switching and augmentation strategies of ADs and non-ADs including lithium and atypical antipsychotics was explained. The second session introduced the placebo- and nocebo-effect with illustrative examples to emphasize the potency of these effects. Furthermore, the nocebo-effect was declared to be immanent in major depression referring Beck’s cognitive triad. Thus, expectancies were highlighted as one conditional part of placebo- and nocebo-effects (4) and being aware of these effects could ultimately improve expectancies and thereby depressive symptoms. The third session started with the fact that expectancies are shaped by experiences, and the patients were encouraged to share their experiences with AD-treatments. Negative experiences were modified if possible, and positive

experiences were reinforced. Participants were motivated to share positive experiences and expectations also outside the group therapy and should not focus solely on negative experiences and expectations. In the last session, the concept of classical conditioning was introduced as another conditional part of placebo- and nocebo-effects (4). Pavlov's dogs were discussed, and it was worked out that every animal life is programmed for Pavlovian conditioning which is also true for human pathological conditions, such as pain and depression. Open and mindful intake of AD and a careful handling of AD were recommended. As part of every session, new members were introduced to enhance group cohesion. In addition, the results and topics of the last session were revised before going into the new topic. At the end of each session the results were summarized and combined with reassurances as portrayed by Hautzinger (5).

These brief group-sessions should systematically optimize the AD-effectiveness by (i) positive information (enhancement of the positive expectation element of the placebo-effect of AD) and (ii) sensitization to the negative suggestion-effects of said, read or heard adverse reactions (attenuation of the negative expectation element of the nocebo-effect of AD) (4). In addition, we intended to improve the therapist-patient-alliance (another mediator of the placebo-effect) as all PE^{+}/NE^{-}-group-sessions were guided by the same therapist (BBC) who was empathetic and had a positive attitude to the effectiveness of ADs (6).

Novel Outcome Measure

To assess a key-element of the placebo- and nocebo-effect more directly we developed the "questionnaire for expectancies regarding medication" (QEM). It was constructed to measure the change in patients' expectancies over time in three domains: size of change (no change at all vs. full recovery), certainty (or confidence) of change (unsure vs. to be absolutely sure that something will change) and speed of change (immediately vs. by and by). These three domains can be judged on three, individual visual analogue scales with scores between 0 and 100 percent for each scale. The QEM was included into the weekly self-report battery consisting of BDI-II, SHAPS-D and WHO-5.

Data collection

Data were collected at visits which were performed by BBC or other hospital psychologists at baseline (visit 1), and then once weekly thereafter (visit 2-4). Each visit comprised completing HAMD, CGI-S and the battery of self-reports (BDI-II, SHAPS-D, WHO-5, QEM). Also, the antidepressant pharmacotherapy was documented.

Sample size, randomization and blinding, data analysis

Sample size for classical frequentist inference was determined with G*Power (30). The test family was an F-Test and the statistical procedure a repeated measures analysis of variance to examine a within-between interaction. The effect size was hypothesized to be Cohen's f = .15 (small to medium effect), the alpha level was set to the standard of .05 and power to .8. Two groups were monitored over 4 measurements. Correlation and sphericity correction was guessed to be r = .70 and ε = 1, respectively. The resulting sample size was n = 38.

A randomization plan was made with Microsoft Excel (version 1803, build 9126.2152) and the function =RANDBETWEEN(0;1) which randomly generated 1, 0. The randomization to CG and EG was performed by an independent person who was not further involved in the study. The HAMD and the CGI-S were rated by various psychologists working in the hospital. Blinding of patients appeared to be impossible regarding the add-on-design of this study and the specific content of the added sessions. Given the real-life-conditions of our study, this study design issue is inevitable and co-terming the pragmatic approach (7,8). On the other hand, we think that unblinded patients as well as an unblinded therapist guiding the PE^{+}/NE^{-}-group-sessions (see above) were definitely not disadvantageous as we wanted to maximize the placebo mechanism of ADs in clinical practice (4).

Data were expressed as mean (standard deviation). Intention-to-treat (ITT)-analysis was performed with all patients included. We did not need to perform a modified ITT-analysis because all included patients gave back the battery of baseline tests. Frequentist and Bayesian analyses were carried out in Jeffrey's Amazing Statistics Program (JASP, 9). Figures were created with R (9) and the package ggplot2 (9). For this study we analyzed the data with the last observation carried forward (LOCF) method. As measures of effect size, we computed Hedges' g* and Cohen's d. For

interpretation we referred to Cohen, thus indicating effect sizes between .2 and .5 as small, effect sizes between .5 and .8 as medium and effect sizes above .8 as large. For correlation analyses (carried out in SPSS, version 24), we interpreted coefficients between .1 and .3 as small, between .3 and .5 as medium and correlation coefficients (here Pearson´s r) above 0.5 as large. For the primary outcome measure BDI-II, we also computed the number needed to treat (NNT) with an event defined as a symptom reduction of at least 50%. To examine the participant's data, we used a 2 by 4 factorial repeated measures analysis of variance (ANOVA) with the between-subjects factor "experimental condition" with two levels (CG vs. EG) and the within-subjects factor "time" with four levels (weeks 1–4). We also conducted a Bayesian 2 by 4 factorial repeated measures ANOVA (10,11). The effect of interest was the interaction effect of the factors "experimental condition" with two levels (CG vs. EG) and time. Thus, we computed the Bayes-factors for all possible models and compared the Bayes-factors of the model including both main factors without interaction against the model with the interaction and reported the resulting Bayes-factor as proposed by Wagenmakers, et al. (10). We interpreted the Bayes-factors according to Lee and Wagenmakers (11) as follows: a Bayes-factor between 1 and 3 represented anecdotal evidence for the candidate model, a factor between 3 and 10 represented moderate evidence, a factor between 10 and 30 represented strong evidence, a factor between 30 and 100 represented very strong evidence and a factor above 100 represented extreme evidence. Because a simple effects-analysis is not readily available for the Bayesian framework, we conducted directed Bayesian t-Tests for all clinical outcomes at study-endpoint to assess the likelihood of a difference at that time. The same statistical tests, i.e. classical and Bayesian, were carried out for the three QEM-domains. For all tests, $p < 0.05$ as significance criterion was used. Moreover, we wanted to examine the influence of patients' gender, age and number of comorbid diagnoses on the relation between patients' expectancies and their outcome scores at study-endpoint. Therefore, we conducted partial correlation analyses between both influential expectancy domains of the QEM (size and certainty of change) and all dependent variables (BDI-II, HAMD, CGI-S, SHAPS-D and WHO-5) which was controlled for gender, age and number of comorbid (ICD-10 F) diagnoses. Furthermore, we conducted a mediation-analysis with EG as independent variable, BDI-II-score at study-endpoint as dependent variable and expected certainty of a change by AD-use as potential mediator. We used the

PROCESS Macro (model number 4) by Hayes (12). To analyze the clinical (as opposed to the statistical) significance of the results we used the methods introduced by Jacobson et al. (7). Clinical significance analyses (see below) were done with the package clinsig (13).

Acknowledgement

We thank the patients for participating in this study. We would like to cordially thank Heath McAnally, MD, MSPH, Medical Director, Northern Anesthesia & Pain Medicine, LLC, Eagle River, AK, USA, for checking the language of the letter.

Statement of Ethics

This single-center 4-week pre-post pragmatic parallel-group randomized study was conducted from May to September of 2018 in the psychiatric ward of the Evangelisches Krankenhaus Castrop-Rauxel, was in accordance with the revised declaration of Helsinki and was approved by the local ethic committee of the Medical Faculty of the University of Duisburg/Essen, Germany. Written informed consent was obtained from participating patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

None

References

1. Klinger R, Flor H. Clinical and Ethical Implications of Placebo Effects: Enhancing Patients' Benefits from Pain Treatment. In: Benedetti F, Enck P, Frisaldi E, Schedlowski M, editors. Placebo. Berlin, Heidelberg: Springer-Verlag; 2014. p. 217–35 (Handbook of Experimental Pharmacology; vol. 225).

2. Sliwinski J, Elkins GR. Enhancing placebo effects: Insights from social psychology. Am J Clin Hypn 2013; 55(3):236–48.

3. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 2008; 5(2):0260-0268.

4. Evers AWM, Colloca L, Blease C, Annoni M, Atlas LY, Benedetti F et al. Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. Psychother Psychosom 2018; 87(4):204–10

5. Hautzinger M. Depressive Störungen: Beruhigende Versicherungen [M34.1]. In: Meinlschmidt G, Margraf J, Schneider S, editors. Lehrbuch der Verhaltenstherapie, Band 4: Materialien für die Psychotherapie. Berlin, Heidelberg: Springer-Verlag; 2012.

6. Norcross JC, Lambert MJ. Psychotherapy relationships that work III. Psychotherapy 2018; 55(4):303–15.

7. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991; 59(1):12–9.30.

8. Roland M, Torgerson DJ. Understanding controlled trials: What are pragmatic trials? BMJ 1998; 316(7127):285.

9. JASP Team. JASP (Version 0.9.0.1) [Computer software]; 2018. Available from: URL: https://jasp-stats.org/.

10. Wagenmakers E-J, Love J, Marsman M, Jamil T, Ly A, Verhagen J et al. Bayesian inference for psychology. Part II: Example applications with JASP. Psychon Bull Rev 2018; 25(1):58–76.

11. Lee MD, Wagenmakers E-J. Bayesian Cognitive Modeling: A Practical Course. Cambridge: Cambridge University Press; 2014.

12. Hayes, A.F. Mediation, Moderation, and Conditional Process Analysis. (2nd ed.). New York: Guilford Press; 2018.

13. Lemon J. clinsig: Clinical Significance Functions [R package version 1.2]; 2016. Available from: URL: https://CRAN.R-project.org/package=clinsig