PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Expectation focused and frequency enhanced cognitive behavioral therapy for patients with major depression (EFFECT): A study protocol of a randomized active-control trial
AUTHORS	Ewen, Anne-Catherine; Bleichhardt, Gaby; Rief, Winfried; Von Blanckenburg, Pia; Wambach, Katrin; Wilhelm, Marcel

VERSION 1 – REVIEW

REVIEWER	Bruijniks, Sanne J E University of Freiburg
REVIEW RETURNED	03-Nov-2022

GENERAL COMMENTS	The authors describe an interesting study protocol testing the effects of a new potential psychotherapy towards an established psychotherapy. However, the rationale for their study design (why not once versus twice EFPI?) and information on why and how certain outcomes are included/not included should be improved (for example: is alliance used as a potential mediator or an outcome?). Also, the exact differences and overlap between study manuals should be made more clear. Small comments on strength and limitation section page 3: 1. page 3: the use of the word naturalistic is a bit confusing because it is in contrast with the definition of an RCT; consider leaving this term out 2. page 3, point 2: I do not understand this sentence, what is exactly meant her? 3. The study is described as practice-oriented, but its absence is also mentioned as a limitation. This is a bit contrasting. Theoretical background: 1. Page 4: Please elaborate on what is meant here, I am not sure what this means or how this is backed up by literature: 'However, treatment research that focuses on theory-based factors might have reached its limits' 2. It should be defined what is meant with 'common structural variables', maybe introduce this concept a bit more elaborately 3. Is there any literature on whether increasing the number of sessions is helpful? It would be nice to read more about this 4. Is there any literature on the role of expectation changes as a mediator? 5. I would like to have a more explicit introduction of the expectation based psychotherapy: how does the role of expectations relates to the other oft hypothesized mechanisms of change (BA, CT) in CBT? How is this integrated in the CBT protocol? Have there been any comparisons between CBT procedures and expectation procedures before? Is there already any literature on the role of expectation based techniques in

	psychotherapy (i.e., its relation with outcome)? Why would the EFPI lead to better results than standard CBT? 6. The trial seems to have rather two separate goals: compare session frequency, and evaluate the EFPI intervention. The introduction should give more rational for why CBT was chosen as an intervention (an not another psychotherapy for depression). Also, why did the authors not compare EFPI once weekly versus EFPI twice weekly? I am also wondering if there are any hypotheses about differential mediators in the CBT versus the EFPI condition. Methods: 7. The study is using a personalized CBT protocol. How does this module relate to the effects of CBT in the literature? Why was this manual chosen? Why was the CBT 24 sessions (as this contrasts the original protocol of Beck)? 8. EFPI: behavioral experiments normally are also part of the CBT protocol. How does this study investigate what is explaining the effect of EFPI? Is no difference is found, can the similar procedures in the protocols be an explanation? 9. I am wondering why the authors choose to only include specific outcomes (under secondary outcomes) for EFPI and not CBT. 10. Is therapeutic alliance include as a potential mediator? Are mediation models planned? 11. I would like to have more explanation on the 6 sessions for the health insurance, what does this mean? What techniques are used in these sessions? 12. I think it would be nice to have an attachment that gives an overview of all procedures/elements in both treatment protocols (so it is more easy to compare and see how the protocols differ or are similar in some ways) Discussion: 13. Considering all limitations, would it not be possible to first pilot the EFPI in a few patients (and test feasibility) before spending so much time and effort in a RCT?

REVIEWER	Kuroki, Toshihide Kyushu University, Clinical Psychology
REVIEW RETURNED	02-Jan-2023

GENERAL COMMENTS	The investigators of this study hypothesize that expectations may be the core mechanism of psychotherapy rather than frequency of sessions and are going to perform randomized-controlled trial to allow comparisons between the following treatment conditions: CBT (1 session/week), condensed CBT (2 sessions/week), and expectation focused psychological interventions (EFPI) (2 sessions/week). Although the study design proposed here is very interesting in elucidating the mechanisms of psychotherapy, there is some question as to whether the hypotheses are generalizable. In particular, the following points needs careful consideration. 1. Since the hypothesis is based on the authors' previous series of research results, a little more explanation of the rationale is needed. For example, what is the ViolEx-model (page 6)?. Isn't it the ViolEx 2.0 model (Panitz et al., Frontiers in Psychology 2021.726432)? 2. Study design and procedure (page 8): The authors address that participants are randomly assigned to one of the three group and assigned to a study therapist. How many therapists give treatment in total? Although practically impossible, it would be ideal for only one therapist to be involved in all treatment procedures. Specify

	what steps the authors have taken to correct for differences among therapists in personal impact on expectations.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sanne J E Bruijniks, University of Freiburg

Comments to the Author:
The authors describe an interesting study protocol testing the effects of a new potential psychotherapy towards an established psychotherapy. However, the rationale for their study design (why not once versus twice EFPI?) and information on why and how certain outcomes are included/not included should be improved (for example: is alliance used as a potential mediator or an outcome?). Also, the exact differences and overlap between study manuals should be made more clear.

First of all, thank you very much for the conscientious work and review. We adapted the manuscript based on your comments and we think that we could really improve it.

Small comments on strength and limitation section page 3:
1. page 3: the use of the word naturalistic is a bit confusing because it is in contrast with the definition of an RCT; consider leaving this term out

You are right that could be misleading. We decided to leave it out.

2. page 3, point 2: I do not understand this sentence, what is exactly meant her?

We reformulated the key point:
„the results will add important information to the research body of structural conditions for psychotherapy, allowing further conclusions on how often psychotherapy should be offered
“ (p.3)

3. The study is described as practice-oriented, but its absence is also mentioned as a limitation. This is a bit contrasting.

Thank you for that point. We reformulated the sentence:

“As this is a manualized psychotherapy study designed for depression, the transfer of results to other disorders may be limited
” (p.4)

Theoretical background:
1. Page 4: Please elaborate on what is meant here, I am not sure what this means or how this is backed up by literature: ‘However, treatment research that focuses on theory-based factors might have reached its limits’

We reformulated the sentence to make it clearer. We wanted to reference to the dodo bird verdict and the upcoming interest of the research to analyze common factors in the different therapy procedures:

“However, treatment research that compares the different psychotherapy procedures with different theoretical backgrounds with the goal to find the best techniques might have reached its limits [8].” (p. 4)

2. It should be defined what is meant with ‘common structural variables’, maybe introduce this concept a bit more elaborately

We included some examples:
“Furthermore, the consideration of common structural variables such as number of sessions, duration of sessions, or environmental factors was rather neglected.” (p. 4)

3. Is there any literature on whether increasing the number of sessions is helpful? It would be nice to read more about this

We included some more articles, showing that the increase of the session frequency is leading to a faster recovery:

“Some studies already showed a positive effect of higher session frequency leading to faster recovery [23-25]. Erekson and colleagues [25] show for example in a naturalistic setting, that a counseling session every week compared to a decreased frequency not only leads to a faster change, but also to a higher likelihood to achieve recovery and to achieve it sooner. Moreover, these findings could also be supported by an RCT comparing one versus two sessions per week, concluding that twice weekly sessions in clinical practice could improve treatment outcome in depression [13].” (p. 5)

4. Is there any literature on the role of expectation changes as a mediator?

Some researchers are arguing and defining expectations as an important mediator/moderator in therapy (see placebo research), however, research about mediating/ moderating effects of expectation change is lacking. Some first experiments are showing a link between a lack of expectation change (i.e., immunization) and depressive symptoms (see articles from Kube et al. – p. 7 in the manuscript). This goes also in line with the research about higher cognitive/ psychological rigidity in f.ex. depressed people, showing a lack of adaptation (f. ex. Hayes et al., 2012, Liknaitzky et al., 2017). A well-constructed mediation analysis is not published yet, whereby research rather seems to focus on the direct relations, as for example the longitudinal study of Kirchner et al. (2022) showing that social rejection expectations predict depressive symptoms and vice versa. However, the ViolEx 2.0 model is suggesting a mediation.

“They also influence the experience in future situations, as it is well-observed in the so-called placebo effects [39-41]. Some studies analyzed the relationship between initial expectation change and treatment outcome [46-48]. As already mentioned above, initial positive outcome expectations are associated to a better treatment outcome, whereas inducing positive outcome expectations or changing negative ones change significantly the treatment outcome in a positive way. Thus, expectations play a central role in psychotherapy, regarding the therapy outcome [49, 50] or the therapeutic relationship [51, 52].” (p. 6)

5. I would like to have a more explicit introduction of the expectation based psychotherapy: how does the role of expectations relates to the other oft hypothesized mechanisms of change (BA, CT) in CBT? How is this integrated in the CBT protocol? Have there been any comparisons between CBT procedures and expectation procedures before? Is there already any literature on the role of expectation based techniques in psychotherapy (i.e., its relation with outcome)? Why would the EFPI lead to better results than standard CBT?

Based on the comment of the other reviewer, we explained the violEx model in more detail, which explains a bit more the rational of the expectation-based interventions. Additionally, we included more articles describing the direct change of expectations and the treatment outcome (see comment before). There are no studies directly comparing expectation procedures and CBT procedures. However, there is a growing branch of literature on interventions that directly address expectations in therapy (f. ex. Initial outcome expectation and real outcome f. ex. Laferton et al.). We integrated the following paragraph to make it clearer, why we hypothesize EFPI to be effective (adequate overview in article of Rief et al, 2022):

“Moreover, making information processing mechanisms (i.e., not only assimilation but also immunization) salient in psychotherapy allows the patients to not only change unhelpful expectations but also learn to actively influence their processing mechanisms. According to Rief and colleagues [53], effective therapy needs to include successful expectation violations to change dysfunctional expectations that are related to the development and/ or maintenance of psychopathology (as for example negative outcome expectations in depression[61, 67, 68]). Based on this rational, therapy resistance may be counteracted by directly addressing immunization processes that are hypothesized to play a crucial role [70]. All these processes described by the ViolEx-model are usually not directly addressed in psychotherapy.” (p.8)

6. The trial seems to have rather two separate goals: compare session frequency, and evaluate the EFPI intervention. The introduction should give more rational for why CBT was chosen as an intervention (an not another psychotherapy for depression). Also, why did the authors not compare EFPI once weekly versus EFPI twice weekly? I am also wondering if there are any hypotheses about differential mediators in the CBT versus the EFPI condition.

In the discussion, we thematize the point, why we are not comparing EFPI once vs. twice weekly (p. 17: As the EFPI treatment is still in its pilot phase as well as to avoid underpowered samples, we opted against a 2 x 2 design, and for the neglect of an EFPI once weekly condition.). As we hypothesize that psychotherapy twice weekly is better than once weekly, we draw from this, that twice weekly EFPI will also be better than once weekly EFPI.
Similar to classic CBT, EFPI is grounded in classical learning theories. The more engagement with a topic, the more is learned (Eaton, 2011; Hall, 1954). A good evidence-based example presents language learning (Ellis, 2002; Ellis & Ferreira-Junior, 2009; Solomon & Howes, 1951) In that context, as EFPI addresses learning mechanisms such as accommodation, it seems reasonable to choose two sessions of EFPI per week over one.

We included the hypothesis of the analysis of potential moderator. We can imagine, that expectation change can moderate or even mediate therapy outcome, but until now, we don’t have a good operationalization (whereas the newly constructed questionnaire IMS may be used for future research about potential mediations of expectation change on treatment outcome). Base on the existing literature, we formulated this hypothesis:

“4. Dysfunctional expectations will have a higher impact on the outcome in the EFPI condition than in the CBT condition.“ (p. 9)

Methods:
7. The study is using a personalized CBT protocol. How does this module relate to the effects of CBT in the literature? Why was this manual chosen? Why was the CBT 24 sessions (as this contrasts the original protocol of Beck)?

Thank you for the comment, we included this to the manuscript to make it clearer, that the manual is on the most common CBT manuals:

„The manual is based on the most common CBT manuals, which are already implemented in practice [76-78].” (p. 12)

The twenty-four sessions were chosen, because the health insurance in Germany is defines short-term therapy as 24 sessions. We hope to get a closer look at the mechanisms of change by utilizing a longer therapy protocol. The more, we therefore chose to include a measurement point at 20 sessions to be consistent with literature (and following Bruijniks et al including 20 sessions). Moreover, in the theoretical background section, we included literature showing, that a number around 20 is appropriate to expect recovery (i.e., 26 sessions leading to 75% recovery).

„Twenty-four sessions are chosen to match the German health care plan of a short-term therapy and is in line with the literature presented in the introduction about the number of session needed to expect recovery.“ (p. 10)

8. EFPI: behavioral experiments normally are also part of the CBT protocol. How does this study investigate what is explaining the effect of EFPI? Is no difference is found, can the similar procedures in the protocols be an explanation?

Good point, we allow also classical behavioral experiments in the CBT condition, however, they are not mandatory in every session and in the standard way of cognitive therapy (not expectation focused). The EFPI condition focuses on the understanding of the information processing mechanisms of oneself and taking control over these by learning to question proper expectations, whereby the main goal of behavioral experiments in CBT is to change dysfunctional thoughts. The behavioral experiments in the EFPI conditions are rather a new information processing strategy that should be learned to the patients rather than a strategy to change the content of expectations. We integrated this expectation into the manuscript:

“In contrast to the possible performed behavioral experiments in the CBT condition, the focus in the EFPI condition lies on the understanding of the information processing mechanisms and, consequently, taking control over these by the possibility to actively influence them. The behavioral experiments in the EFPI condition are a new information processing strategy learned to the patients, rather than a strategy to change the content of expectations.“ (p.13)

9. I am wondering why the authors choose to only include specific outcomes (under secondary outcomes) for EFPI and not CBT.

All outcomes will be investigated in all conditions. There is only one EFPI specific outcome of depressive expectations (DES), which is also interesting regarding its course in the CBT conditions.

10. Is therapeutic alliance include as a potential mediator? Are mediation models planned?

This is a very good point-We now explicitly include moderator and mediator analyses (see point 6, p. 9 in the manuscript). Therapeutic alliance is measured with the Helping Alliance Questionnaire (HAQ).

11. I would like to have more explanation on the 6 sessions for the health insurance, what does this mean? What techniques are used in these sessions?

The goal of the six session is to gather information on the case and to establish a therapeutic relationship. Information is required about the symptomatology, sociodemographic and biographical factors and a functional analysis. Most importantly, no interventions take place during these sessions. We included the following sentence:

“They consist out of anamnesis (e.g., with the help of lifeline) and information gathering to draw a micro and macro functional analysis [71]. There are no interventions allowed during the run-in phase. “ (p.10)

12. I think it would be nice to have an attachment that gives an overview of all procedures/elements in both treatment protocols (so it is more easy to compare and see how the protocols differ or are similar in some ways)

Good idea, we will include an attachment file with the interventions of the study. (see attachment)

Discussion:
13. Considering all limitations, would it not be possible to first pilot the EFPI in a few patients (and test feasibility) before spending so much time and effort in a RCT?

This is a good point. Actually, we tested the manual firstly on feasibility by executing it in a first step and adapting it to the experience made. We integrated a sentence to the method section:

„Even though the EFPI manual is based on cognitive-behavioral interventions, it was decided to test the manual for feasibility first. Therefore, two therapists in training executed the manualized therapy with two voluntary patients and constantly consulted with the supervisor and the patient. The manual was slightly updated based on the comments of the therapists, supervisor, and patients.“ (P. 12)

Reviewer: 2
Dr. Toshihide Kuroki, Kyushu University
Comments to the Author:
The investigators of this study hypothesize that expectations may be the core mechanism of psychotherapy rather than frequency of sessions and are going to perform randomized-controlled trial to allow comparisons between the following treatment conditions: CBT (1 session/week), condensed CBT (2 sessions/week), and expectation focused psychological interventions (EFPI) (2 sessions/week). Although the study design proposed here is very interesting in elucidating the mechanisms of psychotherapy, there is some question as to whether the hypotheses are generalizable. In particular, the following points needs careful consideration.

1. Since the hypothesis is based on the authors' previous series of research results, a little more explanation of the rationale is needed. For example, what is the ViolEx-model (page 6)?. Isn’t it the ViolEx 2.0 model (Panitz et al., Frontiers in Psychology 2021.726432)?

Yes, you are right, the ViolEx model was adapted, especially in precising the involving factors. The basic components however remained the same, so for the intervention planning, it would not make any difference on what model it is based on. However, we precised the model in the manuscript and included the adapted model:

“The ViolEx-model [11, 43], adapted by Panitz and colleagues in 2021 [45], describes the different processes of expectation adaptation or persistence and transfers it to psychopathology. The model hypothesizes that general expectations are formed by the social environment, individual differences (e.g., personality traits), and past experiences. These general expectations are forming situation-

specific expectations. Furthermore, different anticipatory reactions are described to highlight different processes influencing the situational outcome (e.g., attention steering to expectation-confirming cues rather than to expectation-disconfirming cues). A differentiation between internal (i.e., preparation to the situation) and external reactions (i.e., assimilation, or experimentation, approach, or avoidance) are made. Assimilation is described as the process of the attempt to confirm the expectation whereby the experimentation is defined as the process of wanting the openly collect valid data to check the proper expectation. Transferring this to psychopathology, assimilation can include avoidant behavior as for example well known in anxiety disorders [47, 48]. Experimentation is a process that is desired in psychotherapy to adapt dysfunctional or unhelpful thoughts [49, 50]. In a next step, if the expectation is violated through an unexpected experience, the initial expectation should be adapted or at least questioned (i.e., accommodation). This process is often blocked, especially in patients with depression [62]. The ViolEx raises a concept called cognitive immunization, which can lead to expectation persistence." (p.6-7)

2. Study design and procedure (page 8): The authors address that participants are randomly assigned to one of the three group and assigned to a study therapist. How many therapists give treatment in total? Although practically impossible, it would be ideal for only one therapist to be involved in all treatment procedures. Specify what steps the authors have taken to correct for differences among therapists in personal impact on expectations.

Thank you for that good comment. We are not able to determine how many therapists will be involved. We try to keep the number as low as possible regarding. We tried to include more explanation into the manuscript:

"All therapists will receive a standardized training and are scheduled to deliver treatment in all three conditions at least once to balance out therapist effects." (p. 10)

VERSION 2 – REVIEW

REVIEWER	Kuroki, Toshihide Kyushu University, Clinical Psychology
REVIEW RETURNED	10-Mar-2023

GENERAL COMMENTS	The resubmitted manuscript has been appropriately revised according to the reviewers' comments. Therefore, I have no hesitation in accepting this paper for publication in the journal.

VERSION 2 – AUTHOR RESPONSE