

Response to Reviewers' Comments:

We thank the reviewers for their scrutiny of the manuscript and insightful remarks, their good feedback on our study was very encouraging. We hope to match their thoroughness and detail in our reply. Please, note that our replies are written in italics and that any changes to the text are additionally underlined.

Reviewer #1:

I can recommend for a publication in WJP. The topic is interesting, informative and useful for a clinician. The paper is clearly written. It needs some minor changes and explanations before publication:

1. The CBT is well known abbreviation but abbreviations can not be used in the title, so I do suggest to write it in full as Cognitive Behavioural Psychotherapy for Auditory Hallucinations.

Response:

We thank the reviewer for the comment. Title has been amended as follows:

Cognitive Behavioural Therapy for Auditory Hallucinations in Schizophrenia: a review

2. Materials and methods: For the reader it will be very useful the description about the antipsychotics, if the dosages were stable or not in all of the studies.

Response:

We agree with the reviewer, this is an important issue. Antipsychotic medications were provided as part of the treatment as usual and the dosages were changed as clinically required for the two RCTs considered and for most of the non-randomized studies.

In the table 1s of included studies, under "Focus treatment", we have now included how medications were given and the mean dosages in equivalents with the standard deviations, if reported in the primary studies.

Reviewer #2:

Title "An overview of recent findings on CBT for Auditory Hallucinations in Schizophrenia"

It is a review of eight articles suggesting that Cognitive-Behavioral Therapy (CBT) is a useful treatment for reducing compliance with harmful command hallucination. Authors underline that they found some preliminary evidence for the efficacy of CBT in the treatment of command hallucinations.

1. It seems difficult to understand what the Authors intend when they speak of "reducing compliance" with harmful command hallucination. They should clarify.

Response :

Thank you for your request for clarification. We have amended the text (section Introduction) according to this suggestion as follows:

Specifically, CBT applied to the treatment of command hallucinations does not focus on reducing the experience of voices, but on reducing the perceived power of voices to harm the individual and to motivate compliance^[8,22]. Indeed, the main rationale is that by challenging key beliefs about the power of commanding voices, the patients would show a lower level of compliance and appeasement behavior and an increase in resistance to the same voices.

2. It should be interesting to know the antipsychotic drugs (names and dosages) associated to CBT to know the possible combination effects of some specific molecule. Or was the CBT the unique therapy? It is not credible.

Response:

We agree with the reviewer, this is an important issue. Antipsychotic medications were provided as part of the treatment as usual and the dosages were changed as clinically required for the two RCTs considered and for most of the non-randomized studies.

In the table 1 of included studies, under “Focus treatment”, we have now included how medications were given and the mean dosages in equivalents with the standard deviations, if reported in the primary studies.

Reviewer #3:

Apart from the critics below - the manuscript need spelling and grammar correction. Otherwise it is overall a valuable contribution to clinical practice. Review an overview of recent findings on CBT for Auditory Hallucinations in Schizophrenia

1. Title It is not recommendable to use abbreviations in a title. The word “recent” should be avoided, it loses rapidly its actuality. Furthermore, a lengthy title attract less attention. The title would merit from being shorter and spell out CBT. (i.e. Cognitive behavioral therapy for auditory hallucinations in schizophrenia, a review.)

Response :

Thank you for this comment. Title has been amended as follows:

Cognitive Behavioural Therapy for Auditory Hallucinations in Schizophrenia: a review

2. Introduction Third line “related psychotic disorders” is a vague label. Delusional disorders typically don’t exhibit auditory hallucinations although they are among psychotic disorders. The frequency of AH applies to schizophrenia and the word “related psychotic disorders” should be erased. Some language correction is needed (i.e. “most high”)

Response :

Thank you for highlighting this. In Introduction we have erased “related psychotic disorder”. In addition, we have replaced “most frequent” with highest. We corrected the language where needed.

3- Aim: should be confined to state the objective of the present article and not describe other studies – they should have been mentioned beforehand. Apart from the comments above, the introduction is well written and summarizes the motives for the aim.

Response :

Thank you for this comment. We have amended the text (section Introduction) according to this suggestion as follows:

In a recent meta-analysis, Van der Gaag et al.^[23] showed that CBT is effective in the treatment of auditory hallucinations and delusions. Specifically, individually tailored case formulation CBT showed larger effect-size than broad CBT including standard training programs. However, in this study Va der Gaag et al. ^[23] have considered both the auditory hallucinations that delusions. The aim of our review is to provide an updated overview on the efficacy of CBT interventions in AHs. Specifically, we focus on the efficacy of CBT in reducing command hallucinations.

4- Method It is stated that it is a qualitative review. This should further be explained or omitted. A rationale for the chosen time frame should be given. Has there been a review covering a period before 2011? In the last sentence it is stated that eight studies fulfilled the inclusion criteria. These criteria as well as the exclusion criteria should be given.

Response : Thank you for your request for clarification. We have omitted « qualitative ».

As for the chosen period, we decided to focus on the past five years (2011-2016) in order to focus on the most recent data about the efficacy of CBT in the reduction of auditory hallucinations. In fact, for the previous period, Van der Gaag et al. (2014) had already published a meta-analysis. However, this meta-analysis does not focus specifically on auditory hallucinations. We therefore decided to focus only on the past five years because this is the period in which CBT models specifically targeted on auditory hallucinations were developed.

According this we amended the text (section Methods) as follows:

We decided to focus on the past five years (2011-2016) because this is the period in which CBT models specifically targeted on auditory hallucinations were developed.. In fact, for the previous period, Van der Gaag et al. (2014) had already published a meta-analysis. However, this meta-analysis does not focus specifically on auditory hallucinations.

We have inserted the inclusion/exclusion criteria in Figure 1.

We have amended text (section methods) as follows:

In Figure 1 are represented the search strategy with inclusion/exclusion criteria for the papers.

5. Result A somewhat lengthy but informative result section. The direction of the correlation between outcome and negative symptoms should be given for the Thomas et al study.

Response : Thank you for your request for clarification.

We have amended the text (section Results) according to this suggestion as follows: Only overall negative symptoms showed a significant negative correlation ($r_{pb} = -.60$, $p = .001$) with outcome.

6. In the Hutton and Morrison study the phrase “single case study” should not be used. It refers to an established quantitative method for treatment studies. Instead “case study” should be used.

Response :

Thank you for highlighting this. In the Results section we have erased the word “single”.

7. Conclusions Second sentence should be corrected. Only two studies showed superiority to standard care in some but not all outcome measures. The other studies were observational and did not include controls (except the Mortan study). This sentence should be corrected. Third sentence – the direction of the negative symptom to treatment efficacy should be stated.

Response :

Thank you for your request for clarification.

We have amended the text (section Conclusion) according to this suggestion as follows:

The present review describes the efficacy of CBT in patients with AHs.

In summary, the two RCTs included showed a greater efficacy of CBT compared to standard care on AHs. However, in Shawyer^[24] et al., TORCH participants subjectively reporting greater improvement in command hallucinations compared to Befriending but no significant group differences on primary outcome measure that was level of compliance with harmful command hallucination. In Birchwood et al.^[25] instead, CTCH participants showed an improvement in this measure.

One possible explanation of the discrepancy between the two RCTs in term of efficacy on reducing level of compliance with harmful command hallucinations is that, within the general framework of CBT, different theoretical approach can play a different role on the efficacy of the intervention. Indeed, the two RCTs were built on different theoretical frameworks. The TORCH framework is based on the 'acceptance' of voices by "cultivating the capacity to just notice voices and associated thoughts rather than believing and acting on them". The CTCH focuses on targeting individuals' appraisals, behavior and affect, and not necessarily symptoms. It is based on the nature of the relationship with the personified voice. Therefore, if the voice hearer believes the voice to have malevolent intent, and crucially to have the power to deliver the threat, this can motivate compliance or appeasement behavior. In addition, in Shawyer et al.^[24] the intervention 'befriending' was used as the control condition and it has a similar amount of therapist engagement and expectancy as CBT. This is likely to have resulted in smaller between-group effect sizes respect to Birchwood et al.^[25]. As regards non RCT-studies, all papers included showed reduction on frequency and severity of AHs and distress related to them. However, the lack of content details and on rationales within non-RCTs studies decrease their comparability and therefore the chance to draw final conclusions. In terms of predictive variables, negative symptoms appeared to be the strongest predictor of the treatment efficacy. It may be that negative symptoms are a barrier to treatment specific to hallucinations, although it would be important to verify this association in other studies. However, based on this finding, it is possible to propose that negative symptoms interfere with engagement in therapy, in rapport with the therapist, and completion to homework. This might lead to modifications of CBT to treatment for the presence of negative symptoms, such as the use of more behavioral methods.

Some limitations and strengths should be considered in our review. Firstly, the role and the possible interference of antipsychotic medications with psychotherapy should be further assessed in the primary studies. Secondly, there is a discrepancy of study design and outcome measures between studies, which did not allow a quantitative analysis of the results. Thirdly, most studies are only preliminary and underpowered. Among strengths, we have two RCTs with 241 individuals randomized in total and both of them conclude that CBT may be an alternative for individuals with schizophrenia who experience AHs despite antipsychotic treatment

Overall, several CBT models were tested in the studies included. Apart TORCH and CTCH, Mindfulness approach, PBCT or web-based CBT were used.

We propose that further RCTs are needed. In particular, based on our findings, future studies should be drawn with reference to validated theoretical framework that predicts individuals' compliance with voices and the associated distress, rather than the presence of psychotic symptoms per se. This validated theoretical framework should also consider the role of negative symptoms in predicting the effectiveness of the intervention on AHs

Finally, due to the efficacy and high tolerability and acceptability of RCT-studies, we believe that the treatment with CBT should be integrated into standard care for AHs, taking into account that individuals with AHs and command hallucinations especially, and more in general with psychotic disorders, show often a poor compliance to pharmacological treatments.

8. The description of the different CBT models should be given in the method section and only briefly referred to in the conclusion section.

Response : Thank you for this suggestion. However, we mention the models CBT in the results section and we describe them in detail in the section conclusions. This seems to us very useful for discussion and understanding of our findings

9. A paragraph on limitations and strengths should be included in the conclusion section. One limitation is that the actual antipsychotic medication is not accounted for in this review. It is important information for instance if or if not patients are on clozapine, polypharmacy etc. Another is the discrepancy of methods and outcome measures between studies, a third is that most studies are underpowered. Among strengths, that there are at least two methodologically sound studies and that most of the studies point in the same direction justifying the conclusion that CBT may be an alternative for individuals with schizophrenia who experience AH despite antipsychotic treatment.

Response :

We agree with the reviewer. In accordance with the reviewer's suggestion, we added the following paragraph to the conclusions :

Some limitations and strengths should be considered in our review. Firstly, the role and the possible interference of antipsychotic medications with psychotherapy should be further assessed in the primary studies. Secondly, there is a discrepancy of study design and outcome measures between studies, which did not allow a quantitative analysis of the results. Thirdly, most studies are only preliminary and underpowered. Among strengths, we have two RCTs with 241 individuals randomized in total and both of them conclude that CBT may be an alternative for individuals with schizophrenia who experience AHs despite antipsychotic treatment