Author's response to reviews

Title: Cognitive Behaviour Therapy in Medication-Treated Adults with ADHD and Persistent Symptoms: A randomized controlled trial.

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Author's response to reviews: see over
Dr Sabina Alam,
Senior Scientific Editor,
BMC-series journals,

Dear Dr Alam,

Ref. MS:1540603760528406
Cognitive Behaviour Therapy in Medication-Treated Adults with ADHD and Persistent Symptoms: A randomized controlled trial.

Please find attached the manuscript above, which has been revised to take account of reviewer feedback. We are grateful for the helpful feedback provided by the reviewers and have addressed the points raised as follows:

REVIEWER – YIVA GINSBERG

1. Methods, Participants: The authors could preferably change “Ritalin, Ritalin Uno and Concerta” to generic names and also specify the different formulas, such as immediate-release methylphenidate and extended-release methylphenidate. Were there other stimulants provided except from methylphenidate? If so, please specify (minor essential revision).

We have amended this section as requested, which now states on page 7:

All participants were required to have a clinical diagnosis of ADHD and to be stable on prescribed ADHD medication for at least a month, i.e. stimulants (immediate- or extended-release methylphenidate and amphetamine sulphate), atomoxetine or bupropion.

2. Methods, Participants: The authors could preferably change stimulants to methylphenidate, or specify if other stimulants also were provided, such as amphetamine-salts (minor essential revision).
We have amended this section as requested, which now states on page 8:

At baseline, 42 (77.8%) participants were receiving methylphenidate, 11 (20.4%) were receiving atomoxetine, 5 (9.3%) were receiving bupropion, and 1 (1.9%) was receiving amphetamine sulphate.

3. Methods: It should be easier to grasp the entire procedure if the authors provide a study flow chart (CONSORT) (discretionary revision).

We have appended a flowchart as Figure 1 and referenced this at the end of the Procedure section on page 12. We have of course also amended the numbering of the two subsequent figures.

4. Methods, Measures: Is there anything to report on psychometric properties for the modified K-SADS-PL ADHD section and CGI-ADHD (discretionary revision)?

We have amended page 8-9 Measures as follows:

The Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) ADHD section, present and lifetime version (25) interview measures both ADHD symptoms and impairment on functioning (home, work and relationships) and has been modified for adults and translated into Icelandic. Magnusson et al. (26) found that the K-SADS was reliable and valid and had strong correlation with self-reported and informant rated ADHD symptoms. In the present study current symptoms were rated to measure symptom change.

The Clinical Global Impression (CGI; 27) is a single question where the clinician is asked to rate severity of illness on a 7 point scale (i.e., a score of 1 indicates not being ill and a score of 7 indicates being extremely ill) by comparing the patient to other patients with ADHD. The clinician’s severity score is based on judgment regarding impairment in functioning, symptom severity and distress or coping and is supported by examples of these factors (27). The CGI has shown to correlate well with other ADHD measures (28,29).

5. Methods, Participants and Procedure: Regarding treatment with stimulants: It would be interesting to know the ranges and mean dosages of stimulants used by participants in both groups, before and after the trial, and if they were told to try to keep dosages unchanged during the study period, if possible (discretionary revision).

We have added the following to Paragraph 1 in the Participants section on page 7:

The participants were told to try and keep dosages unchanged during the whole study.

We have reported the range and mean dosages change in a new section ‘Medication Changes’ on page 14 of the Results section as follows:

At baseline, methylphenidate dosages ranged between 18-180mg, with a mean dosage of 60.5mg. By the end of treatment, dosages had been increased for two participants in each condition and decreased for one participant in each condition. The dosage range for methylphenidate was 36-162mg, with a mean dosage of 62.5mg. At three-month follow-up dosages had been increased for one participant in each condition and decreased for two in the CBT/MED condition and one in the TAU/MED condition. The dosage range of methylphenidate at follow-up was 36-108mg, with a mean dosage of 59.4 mg.
6. Methods, the Intervention: The authors revised the R&R2 programme to fit ADHD. In what way was the original R&R2 revised, except from decreasing the number of sessions from 35 to 15? Were the ingredients the same as in the original R&R2 programme, newly developed or modified in some way? What decisions were made during this process on what to keep and what to exclude in the programme to fit ADHD? (discretionary revision).

The R&R2ADHD programme was not adapted specifically for the purpose of this research. This has now been made clearer in the Methods, Intervention section on pages 10 and 11:

R&R2ADHD (33) is a 15 session manualised, programme that was developed in 2007 for youths and adults with ADHD and antisocial behavior.

This programme was delivered according to a manual and the coaches also received directions through training and written guidelines. All R&R2ADHD facilitators had extensive experience in CBT and received training in delivering the programme.

7. Methods, Procedure: Did the authors collect any Adverse Events during the trial? The authors could preferably comment on that and explain why AEs were not collected, or if they were collected, report them (discretionary revision).

This had been added to the Results section on pages 14-15 as follows:

Adverse events were recorded during the trial and one participant in the CBT/MED condition reported severe distress at the end of treatment due to changes in personal circumstances. This participant then received individual treatment and was not assessed at follow-up.

8. Methods, Procedure: The authors could preferably expand a little bit about the control condition of TAU/MED. Were participants asked not to engage in other interventions than medication during the study period? Did other interventions take place? If so, what interventions? It is essential to know more about the comparator in relation to the experimental treatment condition (minor essential revision).

We have added the following to Paragraph 3 of the Procedure on page 12:

The participants in both conditions were not asked to refrain from engaging in other interventions during the study period. Information about other interventions was not collected and thus other treatments were not controlled for.

9. Methods, Procedure: Were the participants of the CBT/MED condition asked not to engage in other interventions during the trial besides the CBT programme and medication? If so, did the authors ask them afterwards to what degree they adhered to this recommendation (discretionary revision)?

Please see above response to point 8.

10. Methods, Statistical analysis and Results section: An intention to treat protocol was followed (analysed as randomized), but how did the authors handle missing values (drop-outs)? Did the authors calculate results both per protocol (completers only) OR by including results from drop-
outs, using an imputation method? It would be most appropriate to report results both ways, and discuss any differences in the Discussion section (minor essential revision).

We have provided this information on pages 12-13 in the Statistical analysis section as follows:

Unadjusted mean scores and standard deviations on each of the outcome measures are provided for the CBT/MED and TAU/MED conditions for the three assessment periods - Time 1, Time 2 and Time 3 (see Table 1). Differences between the two conditions on the outcome measures were not statistically significant at baseline. Nevertheless, in order to reduce error variance an analysis of covariance (ANCOVA) was calculated for each of the dependent variables measuring differences between the conditions in time. The baseline scores therefore served as covariates and scores at Time 2 and Time 3 served as dependent variables. Thus intention to treat analysis (ITT) was conducted. Missing values were not imputed because the ANCOVA calculates outcome whilst adjusting for all baseline data. Between group effect sizes for the outcome assessments were measured using Cohen’s d using unadjusted means for the dependent variables and SD pooled for unequal group sizes. Fischer’s exact test was used to compare proportions of medication changes. Since this study follows an ITT protocol, statistical analysis of the outcome variables were completed for all participants regardless of medication changes.

We have carefully considered the request to conduct two independent analyses using different methodologies (ITT vs per protocol). The findings from the current ITT methodology provide robust results with good effect sizes. This methodology is the more conservative of the two and we therefore consider it unnecessary to extend the paper and complicate the outcome by providing two sets of results.

11. Methods, Statistical analysis: The authors measured effect size by using partial eta squared. Most readers are probably more familiar with effect sizes measured by using Cohen’s d. To make results more interpretable, and to facilitate comparison with results from other trials, the authors preferably should report effect sizes by using Cohen’s d, in addition to, or instead of partial eta squared (minor essential revision).

As requested we have substituted partial eta squared with Cohen’s d. This has been amended in the Statistical Analysis section in the methodology on page 13 (see item 10 response, above), and throughout the results and Table 1. Additionally we have amended the abstract accordingly, in line with the results.

12. Discussion, Limitations: Two limitations are discussed in the Discussion section. However, preferably the authors should include a third limitation. This study compared the experimental treatment condition of CBT/MED with a control condition of TAU/MED. Possibly (see remark nr 8) the control condition comprised medication only, or at the least, not group sessions in combination with individual coaching. Therefore, it would be difficult to disentangle the nonspecific effects from meeting with a group, as well as with an individual coach, from the specific effects of the CBT ingredients, which is to be considered as a limitation. The way this study was performed, the effect size might have been exaggerated if participants of the TAU/MED group experienced less placebo effect (minor essential revision).

We have added to the limitations on page 20:

A further limitation is that the participants in the CBT/MED condition received more attention than the TAU/MED participants during the treatment phase and therefore nonspecific placebo effects could limit the results. However, most changes occurred during the period between the end of treatment and three month follow-up and both conditions did not receive any contact during this period.
REVIEWER – PIA ENEBRINK

13. I would like the description of the flow of participants through the study to be more specific and comprehensive in terms of presenting data on inclusion, exclusion, treatment completers (nr. of sessions completed), and completion of psychiatric evaluation/measures at each post assessments, perhaps in a flow chart.

This has now been added (see the response to point 3, above).

14. Information is needed on whether the treatment groups differed on variables such as demographics, medication and impairment.

We have added the following information on page 11:

*At baseline no statistical difference (two-tailed) was found between the two conditions on dosage size of methylphenidate \((t = 1.126, \text{df} = 40, p = .267)\), atomoxetine \((t = .697, \text{df} = 9, p = .504)\), age \((t = -.439, \text{df} = 52, p = .662)\), or sex \((\chi^2 = (1, N=54) = 0.318, p = .573)\). No statistical differences were found on any of the outcome measures at baseline between the two conditions \((p<.05)\).*

15. More detailed description of completers of treatment and non-completers, and an analysis of those not participating/participating in post assessments.

We have added a section ‘Completion Rate’ to the Results on pages 13-14. In this section we provide information about completers and those who did not participate in post assessments. We also present data comparing completers vs non-completers on the two key baseline measures that were independently evaluated.

*Two participants in the CBT treatment condition and four participants in the control condition did not complete all of the end of treatment assessments. A further three participants in the CBT treatment condition but no participants in the control condition did not complete the follow-up assessments.*

*A total of 35 participants completed self-reported questionnaires at the end of treatment and 32 at three month follow up; 34 participants attended the independent evaluation at the end of treatment and 21 at three month follow-up. To test for possible baseline differences between completers and non-completers a comparison was made on baseline IE measures between those who completed the follow-up measures and those who attended the baseline measures but did not complete all the post assessments (two tailed). For the CBT/MED condition there was no statistical difference at baseline between completers \((n = 8)\) and non-completers \((n = 18)\) on the CGI \((t = .493, \text{df} = 24, p = .626)\) or on the K-SADS \((t = .720, \text{df} = 24, p = .479)\). The same results were found for the TAU/MED condition where no statistical difference was found between completers \((n = 13)\) and non-completers \((n = 12)\) on baseline measures of CGI \((t = .419, \text{df} = 23, p = .679)\) or K-SADS \((t = .480, \text{df} = 23, p = .636)\).*

16. The authors should provide an ITT-analysis.

An ITT protocol was followed, please see the response to item 10.
17. The CBT-treatment manual is nicely described. It would be valuable if the authors provided information on treatment integrity.

We have added the following sentence on page 12:

*Treatment integrity was ensured in two ways; first by adopting a structured manualised CBT programme and, second, via the independent observation of a sample of sessions by a practitioner who monitored adherence to the manualised treatment protocol.*

18. Some additional information on what constituted the TAU, number of sessions, etc, and if the therapists conducting this treatment were other therapists than those in the CBT-condition is needed.

We have clarified the TAU treatment provision on page 11 as follows:

*The TAU/MED condition received psychopharmacological treatment only......... The participants in both conditions were not asked to refrain from engaging in other interventions during the study period. Information about other interventions was not collected and thus other treatments were not controlled for.*

19. RATE-S is not as well-known as the other measures used and its psychometric properties should be more specifically described.

We have added references to the measure’s previous use on page 10 as follows:

*The RATE-S scale has been shown to have good reliability and validity (11,34,35).*

20. Baseline score need not serve as covariates.

We have explained our decision to maintain ANCOVA in the analysis section on page 12 as follows:

*Unadjusted mean scores and standard deviations on each of the outcome measures are provided for the CBT/MED and TAU/MED conditions for the three assessment periods - Time 1, Time 2 and Time 3 (see Table 1). Differences between the two conditions on the outcome measures were not statistically significant at baseline. Nevertheless, in order to reduce error variance an analysis of covariance (ANCOVA) was calculated for each of the dependent variables measuring differences between the conditions in time. The baseline scores therefore served as covariates and scores at Time 2 and Time 3 served as dependent variables. Thus intention to treat analysis (ITT) was conducted. Missing values were not imputed because the ANCOVA calculates outcome whilst adjusting for all baseline data. Between group effect sizes for the outcome assessments were measured using Cohen’s d using unadjusted means for the dependent variables and SD pooled for unequal group sizes. Fischer’s exact test was used to compare proportions of medication changes. Since this study follows an ITT protocol, statistical analysis of the outcome variables were completed for all participants regardless of medication changes.*
21. I don’t think that the following conclusion in the abstract is fully supported by the study due to the lack of “only CBT-treatment-group”: “The implications are that the benefits of R&R2ADHD are multifaceted and that combined psychopharmacological and CBT based treatments may maximize the learning benefits from CBT interventions” The combined treatment may add to and improve the interventions based on medication.

We have amended this section in the Abstract as suggested, and additionally amended the discussion on page 19.

Abstract:

The implications are that the benefits of R&R2ADHD are multifaceted and that combined psychopharmacological and CBT based treatments may add to and improve pharmacological interventions.

Discussion page 19:

Thus the benefits of R&R2ADHD are multifaceted and the combination of psychopharmacological and CBT treatments may add to and improve pharmacological interventions.

Additional changes:

We have provided the trial registration reference at the end of the abstract on page 3.

We look forward to hearing from you.

Yours sincerely,

Dr Susan Young.