

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of home-based non-pharmacological interventions for treating depression: a systematic review and network meta-analysis of randomized-controlled trials
AUTHORS	Sukhato, Kanokporn; Lotrakul, Manoch; Dellow, Alan; Ittasakul, Pichai; Thakkinstian, Ammarin; Anothaisintawee, Thunyarat

VERSION 1 - REVIEW

REVIEWER	Katherine Clarke UCL, United Kingdom
REVIEW RETURNED	10-Oct-2016

GENERAL COMMENTS	<p>This is an excellent review. It is well presented and of clinical importance. I have a few minor suggestions:</p> <p>-In the discussion you make the point that adherence to exercise within the exercise interventions may be low. For this reason, I recommend that throughout the paper you change 'exercise' to 'exercise intervention', for clarity. For example, "our study found no benefit from home-based exercise" (pp 17) should be changed to "our study found no benefit from home-based exercise interventions".</p> <p>-There are a few minor language points/possible errors. page 3, line 11: 'were searched since initiations to 7th August' should read 'were searched from inception to 7th August' page 6, line 48: 'Interested interventions' should read 'Interventions of interest' page 7, line 23: 'Interested interventions' should read 'Interventions of interest' page 8, line 28: 'fix effect model' should read 'fixed effect model' Page 18, lines 7-17: References are not in the correct format</p>
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REVIEWER	Linn Karlsson Institution of Medicine and Health Sciences, Linkoping University, Sweden
REVIEW RETURNED	27-Dec-2016

GENERAL COMMENTS	<p>- The research question could be described more clear. In the title and abstract, the home-base aspect of the interventions is highlighted, but the study rather investigates the efficacy of psychological intervention and/or exercise applied in a home setting compared to interventions in the clinic based on medication or a supporting contact (without specified psychological and/or exercise interventions).</p>
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	<ul style="list-style-type: none"> - In the design, the quality of the studies are based on assessment of bias, but the important and basic aspect of power in the included studies is missing as far as I can see. Please insert this aspect as well. - Research ethics of the included studies are not specified, please insert a short information about the etichs. - Please, describe and motivate the network analyse a bit more - The outcomes of the systematic review could be completmented with effect sizes, in order to make them more clinically useful - In the bullet-point strenghts and limitations of the study, I miss the fact that adherence to the home-based interventions not is investigated. A fact that is in the discussion and probably are essential for the effect of the intervention. - In general: I find this manuscript easy and enjoyable to read. It reveals clinically important aspects for the treatment of depression. The discussion points at several interesting factors, but I miss references in some parts of the discussion. Thank you for good work with this manuscript.
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REVIEWER	Nick Meader University of York, UK
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	<p>Overall I think this is a good systematic review and meta-analyses. I think largely the interpretation is correct however I think the limitations of the data aren't sufficiently acknowledged.</p> <p>1) Comparisons between the interventions assessed through the network meta-analysis are very preliminary. Though at this stage it appears the home based psychological interventions and combined exercise and psychological interventions appear more effective than home-based exercise - I think such findings need to be confirmed in a bigger trial.</p> <p>2) Probably the key issue here is the transitivity or consistency assumption. I think your section on this is too brief and should reflect more on the potential issues. I have a few points on this that need acknowledging in the paper:</p> <p>a) though you do a statistical test - the lack of direct comparisons (I think there was only one) means the findings from these tests have very little power so can't be used to justify the consistency assumption.</p> <p>b) There's a number of factors that may potentially impact on inconsistency for indirect comparisons in your analysis e.g. home visits were included in some usual care groups, differences in types of depression, baseline depression score, antidepressant use, definition of remission. These factors all vary widely between studies and its unclear the extent to which they may contribute to inconsistency.</p> <p>c) more concretely the remission rate in the usual care group appears much higher in trials of home based exercise, and the lowest in the combined psychotherapy and exercise trials. This makes me wonder whether differences between interventions might partly be explained by control event rate.</p>
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	<p>3) Typo - on p13 you mention that home based exercise is 0.03 units lower than the usual care group - I think you mean 1.03 units since SMD is -1.03 rather than -0.03.</p> <p>4) I think its better not to quote the p-values from Egger's test as there isn't sufficient power - or if you want to quote them then at least acknowledge that there are few too studies included for the findings of these statistical test to be meaningful.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Katherine Clarke

Institution and Country: UCL, United Kingdom

Please state any competing interests: None declared

Please leave your comments for the authors below

This is an excellent review. It is well presented and of clinical importance. I have a few minor suggestions:

1. In the discussion you make the point that adherence to exercise within the exercise interventions may be low. For this reason, I recommend that throughout the paper you change 'exercise' to 'exercise intervention', for clarity. For example, "our study found no benefit from home-based exercise" (pp 17) should be changed to "our study found no benefit from home-based exercise interventions".

Ans. We have changed 'exercise' to 'exercise intervention' as your recommendation (see highlighted).

2. There are a few minor language points/possible errors.

- page 3, line 11: 'were searched since initiations to 7th August' should read 'were searched from inception to 7th August'

- page 6, line 48: 'Interested interventions' should read 'Interventions of interest'

- page 7, line 23: 'Interested interventions' should read 'Interventions of interest'

- page 8, line 28: 'fix effect model' should read 'fixed effect model'

- Page 18, lines 7-17: References are not in the correct format

Ans. We have corrected the manuscript as your suggestions.

Reviewer: 2

1. The research question could be described more clear. In the title and abstract, the home-base aspect of the interventions is highlighted, but the study rather investigates the efficacy of psychological intervention and/or exercise applied in a home setting compared to interventions in the clinic based on medication or a supporting contact (without specified psychological and/or exercise interventions).

Ans. The objective of our study was to systematically review all available home-based interventions, not focus only on home-based psychological intervention and exercise. Therefore, we used the search terms such as "home care services", "home visit", and "home treatment" for searching the relevant articles. The results of our searching could be categorized into four groups of intervention (i.e. 1) home-based psychological intervention 2) home-based exercise 3) combined home-based psychological intervention with home-based exercise 4) complementary or alternative medicine). However, the interventions of the included studies were mostly home-based psychological intervention and exercise. We also describe more details of the objectives and results of this study in the introduction and result parts (see pages 5, 6, 10).

2. In the design, the quality of the studies are based on assessment of bias, but the important and basic aspect of power in the included studies is missing as far as I can see. Please insert this aspect as well.

Ans. We have assessed the power of the study and added this domain in the risk of bias assessment (see Supplementary Table 1 and pages 8 and 13). Studies were classified as high risk of bias if they

reported the power to detect the difference less than 80%.

3. Research ethics of the included studies are not specified, please insert a short information about the ethics.

Ans. We have added the information about the ethics in the result part (see page 9).

4. Please, describe and motivate the network analyse a bit more

Ans. We have explained more how a network meta-analysis works in the statistical analysis part (see pages 8 and 9).

5. The outcomes of the systematic review could be complemented with effect sizes, in order to make them more clinically useful.

Ans. We did estimate the treatment effect sizes (i.e. pooled mean difference of depression score between home-based psychological intervention vs usual care (see page 13), combined home-based psychological intervention with exercise vs usual care (see page 14). However, in this revision we already have interpreted the clinical meaning of these effect sizes in the discussion part (see page 17).

6. In the bullet-point strengths and limitations of the study, I miss the fact that adherence to the home-based interventions not is investigated. A fact that is in the discussion and probably are essential for the effect of the intervention.

Ans. We agree with your comment and have added more details about "adherence" in the discussion part (see pages 20 and 21).

- In general: I find this manuscript easy and enjoyable to read. It reveals clinically important aspects for the treatment of depression. The discussion points at several interesting factors, but I miss references in some parts of the discussion. Thank you for good work with this manuscript.

Reviewer: 3

Reviewer Name: Nick Meader

Institution and Country: University of York, UK

Please state any competing interests: None declared

Please leave your comments for the authors below

Overall I think this is a good systematic review and meta-analyses. I think largely the interpretation is correct however I think the limitations of the data aren't sufficiently acknowledged.

1. Comparisons between the interventions assessed through the network meta-analysis are very preliminary. Though at this stage it appears the home based psychological interventions and combined exercise and psychological interventions appear more effective than home-based exercise - I think such findings need to be confirmed in a bigger trial.

Ans. We agree with your comment and have added this point in the limitation (see page 20).

2. Probably the key issue here is the transitivity or consistency assumption. I think your section on this is too brief and should reflect more on the potential issues.

Ans. We have added more information about the consistency assumption in the statistical analysis and discussion parts (see pages 9, 19, and 20).

I have a few points on this that need acknowledging in the paper:

a) though you do a statistical test - the lack of direct comparisons (I think there was only one) means the findings from these tests have very little power so can't be used to justify the consistency assumption.

Ans. As for our network meta-analysis displayed in supplement Figure 5, there were three direct comparisons including 1) home-based psychological intervention vs usual care, 2) home-based exercise vs usual care, and 3) combined home-based psychological intervention and exercise vs usual care. As a result, consistency assumption could be assessed for only these three comparisons; whereas other three indirect comparisons (i.e., 1) home-based psychological intervention versus home-based exercise, 2) home-based psychological intervention versus combined home-based psychological intervention and exercise, and 3) home-based exercise versus combined home-based psychological intervention and exercise) could not be assessed. We have commented on this

limitation in discussion, see pages 19 and 20.

b) There's a number of factors that may potentially impact on inconsistency for indirect comparisons in your analysis e.g. home visits were included in some usual care groups, differences in types of depression, baseline depression score, antidepressant use, definition of remission. These factors all vary widely between studies and its unclear the extent to which they may contribute to inconsistency.

Ans. We have explored the characteristics of study participants and study interventions included in indirect comparisons and have presented this information in Supplementary Table 2. We agree that these factors were heterogeneous between studies and may affect the validity of the consistency assumption. We have discussed and acknowledged this concern (discussion section, pages 19 and 20).

c) more concretely the remission rate in the usual care group appears much higher in trials of home based exercise, and the lowest in the combined psychotherapy and exercise trials. This makes me wonder whether differences between interventions might partly be explained by control event rate.

Ans. Only randomized controlled trials were included in this review. Therefore, the baseline characteristics and prognosis of study's participants were balanced between intervention and control groups in each trial (see Supplementary Table 2). The nature of the intervention itself together with patient adherence to treatment are more likely to play the major role underlying differences in treatment efficacy, rather than being explained by the control event rate. The effect of adherence to treatment have been discuss more in the discussion (see page 20).

3. Typo - on p13 you mention that home based exercise is 0.03 units lower than the usual care group - I think you mean 1.03 units since SMD is -1.03 rather than -0.03.

Ans. We have corrected this mistake (see page 13).

4. I think its better not to quote the p-values from Egger's test as there isn't sufficient power - or if you want to quote them then at least acknowledge that there are few too studies included for the findings of these statistical test to be meaningful.

Ans. We have acknowledged the low power of Egger test in the publication bias section (see page 16).

VERSION 2 – REVIEW

REVIEWER	Katherine Clarke UCL, United Kingdom
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	<p>This is an important and well conducted review.</p> <p>I feel the paper would be improved by a more thorough description of what is meant by 'usual care' in included studies. I do not feel Reviewer 3's comment 2c has been fully addressed: if there are overall differences in the control event rate in a certain group of trials this may well impact the results of the network meta-analysis. The fact that individual studies are randomised does not negate this. Perhaps a more detailed comment on similarities and differences between 'usual care' in the 3 main trial types would allow readers to explore this issue.</p> <p>It is good that the authors have recommended a randomised trial to properly compare the intervention types explored in this review.</p> <p>There are a few spelling mistakes, for example in Supplementary Figure 5.</p>
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REVIEWER	Linn Karlsson Institution of Medicine and Health, Linköping University, Sweden
REVIEW RETURNED	26-Mar-2017

GENERAL COMMENTS	This is an interesting and important manuscript. I find all the points in the checklist to be described properly in the manuscript now. Even if none of the checklistpoints needs a further explanation or elaboration, I want you to observe that there are some parts of the discussion where inclusion of references should be interesting, for example about the elaboration about potential effect mechanisms why exercise is beneficial for depression. Further, I wonder about the definition of home-based; is internet delivered psychological treatment included, and also - the degree of supervision or follow up of the interventions might be interesting, as well as the intensity of the home-based exercise.
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REVIEWER	Nick Meader University of York, UK
REVIEW RETURNED	03-Apr-2017

GENERAL COMMENTS	Thanks for the changes to the text, I think the paper has been substantially improved and comments have mainly been taken into account. A minor issue - some editing of the text would be helpful as there is some awkward phrasing. But overall its well written.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Katherine Clarke

Institution and Country: UCL, United Kingdom

Please state any competing interests: None declared

Please leave your comments for the authors below

This is an important and well conducted review.

I feel the paper would be improved by a more thorough description of what is meant by 'usual care' in included studies.

Ans. We have added information to the definition of usual care in the section concerning treatment comparison (see page 12) and Supplementary Table 2.

I do not feel Reviewer 3's comment 2c has been fully addressed: if there are overall differences in the control event rate in a certain group of trials this may well impact the results of the network meta-analysis. The fact that individual studies are randomised does not negate this. Perhaps a more detailed comment on similarities and differences between 'usual care' in the 3 main trial types would allow readers to explore this issue.

Ans. We agree with your comments and have discussed 'usual care' in greater depth for each of the included studies. This information is summarised in Supplementary Table 2.

In addition, in the discussion section (pages 19 and 20) we have discussed the potential impact of different definitions of usual care among the 3 trial types on the results of network meta-analysis.

It is good that the authors have recommended a randomised trial to properly compare the intervention types explored in this review.

There are a few spelling mistakes, for example in Supplementary Figure 5.

Ans. We have corrected these spelling mistakes.

Reviewer: 2

Reviewer Name: Linn Karlsson

Institution and Country: Institution of Medicine and Health, Linköping University, Sweden

Please state any competing interests: None declared

Please leave your comments for the authors below

This is an interesting and important manuscript. I find all the points in the checklist to be described properly in the manuscript now. Even if none of the checklist points needs a further explanation or elaboration, I want you to observe that there are some parts of the discussion where inclusion of references should be interesting, for example about the elaboration about potential effect mechanisms why exercise is beneficial for depression.

Ans. We have checked and updated references exploring the possible effect mechanisms underlying the benefits of exercise (pages 18 and 19).

Furhter, I wonder about the definition of home-based; is internet delivered psychological treatment included, and also - the degree of supervision or follow up of the interventions might be interesting, as well as the intensity of the home-based exercise.

Ans. We have added the reasons why internet-delivered psychological treatment was excluded from our review in the section about interventions of interest (see page 7). Degree of treatment adherence has been included in Tables 2 and 3. The intensity of home-based exercise for most of the included studies was moderate intensity and we have added this information in the section about home-based exercise intervention (page 11).

Reviewer: 3

Reviewer Name: Nick Meader

Institution and Country: University of York, UK

Please state any competing interests: None declared

Please leave your comments for the authors below

Thanks for the changes to the text, I think the paper has been substantially improved and comments have mainly been taken into account.

A minor issue - some editing of the text would be helpful as there is some awkward phrasing. But overall its well written.

Ans. The manuscript has been reviewed by our native English speaking co-author.