PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cognitive-Behavioral Analysis System of Psychotherapy (CBASP), drug or their combination: Differential therapeutics for persistent depressive disorder: A study protocol of an individual participant data network meta-analysis
AUTHORS	Furukawa, Toshi; Schramm, Elisabeth; Weitz, Erica; Salanti, Georgia; Efthimiou, Orestis; Michalak, Johannes; Watanabe, Norio; Cipriani, Andrea; Keller, Martin; Kocsis, James; Klein, Daniel; Cuijpers, P.

VERSION 1 - REVIEW

REVIEWER	David L. Streiner McMaster University, Hamilton, Ontario, Canada University of Toronto, Toronto, Ontario, Canada Dr. Furukawa studied with me about 20 years ago. We have also published together, although not in the past 10 years.
REVIEW RETURNED	16-Mar-2016

GENERAL COMMENTS	This paper is a protocol for a network meta-analysis comparing cognitive-behavioral analysis system of psychotherapy (CBASP) versus drug or their combination. As would be expected from this excellent team, it is very well thought out and clearly described. However, I would raise a few questions: (1) There are other forms of therapy that have been proven to work with severe depression, including cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT). The originator of CBASP claims that it is not CBT, so would it make sense to compare it against CBT and/or IPT? (2) One of the secondary outcomes is a 50% reduction in depression scores. There are many problems associated with this somewhat arbitrary figure, although it is widely used in psychiatry. A better outcome would perhaps be the Reliable Change Index, which takes into account not only the baseline value, but also the range of normal of the test and its standard error of measurement. (3) Why is gender not one of the predictor variables? (4) The authors state that missing data will be dealt with using imputation under the assumption that the data are missing at random (MAR). However, it is highly doubtful whether the data really are MAR. Many of the variables will not be measured by most studies (e.g., therapeutic alliance, patient preference, or childhood maltreatment). This means that the reason for missingness is related to other variables that differentiate one study from another, such as

	treatments given, possibly the ethnicity of the participants, and so forth.

REVIEWER	Dr Murali Krishna University of Southampton UK CSI Holdsworth Memorial Hospital, India.
REVIEW RETURNED	30-Mar-2016

GENERAL COMMENTS	This is a protocol of a systematic review that will provide better insights into individual characteristics of the subjects and its influence on treatment outcomes from a very specific type of psychotherapy. This study will inform clinical practice and development of services for chronic depression. The following minor points need to be addressed before publication. a. The authors need to present a section on limitations of their protocol . b. Patients with chronic depression are also likely to receive medication other than antidepressants : for e.g benzodiapene, antipsychotics and mood stabilisers. How will these be addressed or accounted ? c. Chronic depression is also associated with alcohol and substance misuse : again authors need to mention how this will be addressed d. Another other important variable of interest is cognition performance/ impairment which is likely to influence the outcome. The protocol must collect information about this if available and examine for its impact on outcomes. This is particularly relevant for studies including older adults. e. A separate section on inclusion and exclusion criteria should be provided, for e.g.. would authors consider the study where depression outcomes are secondary but primary disorder is a physical condition ? language exclusion ? exclusion if individual data not available ? patients on mood stabilisers and antipsychotics ? those with mild cognitive impairment etc. . This is very important if the work needs to be reproduced. f. what is the strategy to minimise or address publication bias and studies from the non western setting (e.g Japanese) g. The odds ratio for drop outs from each study should be collected and pooled odds for the same has to be collated. The protocol team is a group of well established leaders in this field, who will undoubted achieve this in time. However some time lines should be incorporated.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
This paper is a protocol for a network meta-analysis comparing cognitive-behavioral analysis system of psychotherapy (CBASP) versus drug or their combination. As would be expected from this excellent team, it is very well thought out and clearly described. However, I would raise a few questions:

(1) There are other forms of therapy that have been proven to work with severe depression, including cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT). The originator of CBASP claims that it is not CBT, so would it make sense to compare it against CBT and/or IPT?
RESPONSE: Thank you very much for raising this important point. Yes indeed, other forms of

psychotherapy may or may not be differentially effective for chronic depression and/or some subgroups thereof. However, that would be a next step of research. In this study we would like to focus on differential therapeutics of CBASP, pharamacotherapy and their combination. We intend to expand the methodology necessary to carry out such tasks while conducting the current research and then we plan to tackle the important issue raised by the reviewer once we complete the current analysis.

(2) One of the secondary outcomes is a 50% reduction in depression scores. There are many problems associated with this somewhat arbitrary figure, although it is widely used in psychiatry. A better outcome would perhaps be the Reliable Change Index, which takes into account not only the baseline value, but also the range of normal of the test and its standard error of measurement.
RESPONSE: While we agree that RCI is a less arbitrary threshold, being a dichotomous measure, it is likely to be less powerful statistically than the continuous measure from which it is derived. We will use the continuous measure of depression severity as our primary outcome and we intend secondary outcomes to serve as supplementary/complementary indices to facilitate the interpretation of the main findings. We therefore reason that using the conventional threshold of 50% or greater reduction will be clinically more interpretative than using the RCI.

(3) Why is gender not one of the predictor variables?
RESPONSE: First of all, gender was not listed in the comprehensive review of “factors associated with treatment response in two or more studies” by Kessler et al (in press – ref 29 in the manuscript). We further wished to limit the number of variables to be examined in meta-regression as much as possible in order to avoid spurious findings due to multiple testings.

(4) The authors state that missing data will be dealt with using imputation under the assumption that the data are missing at random (MAR). However, it is highly doubtful whether the data really are MAR. Many of the variables will not be measured by most studies (e.g., therapeutic alliance, patient preference, or childhood maltreatment). This means that the reason for missingness is related to other variables that differentiate one study from another, such as treatments given, possibly the ethnicity of the participants, and so forth.
RESPONSE: While this might be true, it would be difficult to account for missing not at random in a meta-analysis with IPD. The most we could do is to run a sensitivity analysis in which we will estimate effect sizes assuming that the missing data is not missing at random and we will employ expert opinion about variables associated with informative missing. We have added this sensitivity analysis on page 10.

Reviewer: 2
This is a protocol of a systematic review that will provide better insights into individual characteristics of the subjects and its influence on treatment outcomes from a very specific type of psychotherapy. This study will inform clinical practice and development of services for chronic depression. The following minor points need to be addressed before publication.
a. The authors need to present a section on limitations of their protocol.
RESONSE: In the Discussion section, we inserted a paragraph where we discussed the limitations of this study protocol as follows: “Possible limitations of this study protocol include the following. First of all, the IPD-NMA will not be able to examine variables that have not been measured in the original studies. We therefore do not yet know if we will be able to examine all or most of the variables that we have listed in this protocol. Secondly, the number of studies eligible for this IPD-NMA may be in themselves limited and it is further possible that we may not be able to obtain all the relevant individual participant data from the relevant studies.” (p. 11)

b. Patients with chronic depression are also likely to receive medication other than antidepressants :

for e.g benzodiapene, antipsychotics and mood stabilisers. How will these be addressed or accounted ?
c. Chronic depression is also associated with alcohol and substance misuse : again authors need to mention how this will be addressed
RESPONSE: Thank you very much for this important suggestion. Although we anticipate that these co-interventions and co-morbidities will be controlled in the original trial protocols, we agree that we should collect information if this is so. And if not, such variables must be incorporated into the analyses. We have therefore listed the relevant variables as independent variables. (p.8 and p. 9)

d. Another other important variable of interest is cognition performance/ impairment which is likely to influence the outcome. The protocol must collect information about this if available and examine for its impact on outcomes. This is particularly relevant for studies including older adults.
RESPONSE: While we agree that the reviewer's point is true in general, we do not anticipate patients with cognitive impairment would be included in trials of psychotherapies such as CBASP. As stated above, we must be careful with the number of variables to be examined in meta-regression in order to avoid spurious findings due to multiple testings. We therefore explicitly listed cognitive impairment as an exclusion criterion (See also our response to the reviewer's comment e.)

e. A separate section on inclusion and exclusion criteria should be provided, for e.g.. would authors consider the study where depression outcomes are secondary but primary disorder is a physical condition ? language exclusion ? exclusion if individual data not available ? patients on mood stabilisers and antipsychotics ? those with mild cognitive impairment etc. . This is very important if the work needs to be reproduced.
RESPONSE: Thank you very much for pointing this out. We added "No language limitation will be employed." and "A concurrent secondary diagnosis of another psychiatric disorder will not be considered as exclusion criterion, but studies in which all participants have a concurrent primary diagnosis of another mental disorder will be excluded. Patients with a serious concomitant medical illness, including cognitive impairment, will be excluded, nor will we include studies where all participants suffer from a primary medical condition." in the Criteria for considering studies in this review (pp. 5-6). The problem of co-prescriptions will be handled as an independent variable in the meta-regression if there are indeed such studies. When the individual participant data are not available, we will use the aggregate data as described in Donegan et al by distinguishing within-trial and between-trials interactions (model 5) (See page 10, Analyses subsection).

f. what is the strategy to minimise or address publication bias and studies from the non western setting (e.g Japanese)
We will not use any language limitation. By using the search methodology as described in the Methods section and also through personal contacts, we anticipate that we will be able to identify all Western and non-Western studies of CBASP using qualified therapists, because CBASP is a relatively new psychotherapy and the training program has been supervised by its developer since the early days (http://www.cbasp.org). However, in order to examine the possible publication bias, we added the following subsection in the Methods section. "To examine the association between small study effects and the potential of publication bias we will employ contour-enhanced funnel plots for pairwise meta-analyses if more than 10 studies per treatment comparison are available 48 and comparison-adjusted funnel plots for network meta-analyses 49. If evidence of publication bias is found, we will incorporate this in the interpretation of results." (p. 9)

g. The odds ratio for drop outs from each study should be collected and pooled odds for the same has to be collated.
RESPONSE: We will calculate a pooled odds ratio for dropouts for any reason as a proxy measure of overall treatment acceptability.

The protocol team is a group of well established leaders in this field, who will undoubted achieve this in time. However some time lines should be incorporated.
RESPONSE: We thank the reviewer's kind words. The time plan for our team is as follows: "We plan to complete the study identification and obtain individual participant data from the relevant studies by the end of 2016, conduct the analyses and submit the manuscript to a peer-reviewed international journal by mid-2017." (p. 11)

VERSION 2 – REVIEW

REVIEWER	David L. Streiner McMaster University Canada
REVIEW RETURNED	15-Apr-2016

GENERAL COMMENTS	I have no further comments. I believe the authors have adequately addressed the concerns raised.