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Cognitive-Behavioural Analysis System of Psychotherapy (CBASP), a drug, or their combination: differential therapeutics for persistent depressive disorder: a study protocol of an individual participant data network meta-analysis

Toshi A Furukawa,[1] Elisabeth Schramm,[2] Erica S Weitz,[3] Georgia Salanti,[4] Orestis Efthimiou,[4] Johannes Michalak,[5] Norio Watanabe,[1] Andrea Cipriani,[6] Martin B Keller,[7] James H Kocsis,[8] Daniel N Klein,[9] Pim Cuijpers[3]

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For numbered affiliations see end of article.

Correspondence to
Professor Toshi A Furukawa; furukawa@kuhp.kyoto-u.ac.jp

ABSTRACT

Introduction: Despite important advances in psychological and pharmacological treatments of persistent depressive disorders in the past decades, their responses remain typically slow and poor, and differential responses among different modalities of treatments or their combinations are not well understood. Cognitive-Behavioural Analysis System of Psychotherapy (CBASP) is the only psychotherapy that has been specifically designed for chronic depression and has been examined in an increasing number of trials against medications, alone or in combination. When several treatment alternatives are available for a certain condition, network meta-analysis (NMA) provides a powerful tool to examine their relative efficacy by combining all direct and indirect comparisons. Individual participant data (IPD) meta-analysis enables exploration of impacts of individual characteristics that lead to a differentiated approach matching treatments to specific subgroups of patients.

Methods and analysis: We will search for all randomised controlled trials that compared CBASP, pharmacotherapy or their combination, in the treatment of patients with persistent depressive disorder, in Cochrane CENTRAL, PUBMED, SCOPUS and PsycINFO, supplemented by personal contacts. Individual participant data will be sought from the principal investigators of all the identified trials. Our primary outcomes are depression severity as measured on a continuous observer-rated scale for depression, and dropouts for any reason as a proxy measure of overall treatment acceptability. We will conduct a one-step IPD-NMA to compare CBASP, medications and their combinations, and also carry out a meta-regression to identify their prognostic factors and effect moderators. The model will be fitted in OpenBUGS, using vague priors for all location parameters. For the heterogeneity we will use a half-normal prior on the SD.

Ethics and dissemination: This study requires no ethical approval. We will publish the findings in a peer-reviewed journal. The study results will contribute to more finely differentiated therapeutics for patients suffering from this chronically disabling disorder.

Trial registration number: CRD42016035886.

Strengths and limitations of this study

- This is the first systematic review and individual participant data network meta-analysis (IPD-NMA) comparing Cognitive-Behavioural Analysis System of Psychotherapy (CBASP), the only psychotherapy specifically developed to treat chronic depression, pharmacotherapy and their combination, for persistent depressive disorder.
- The network meta-analysis enables examination of relative efficacy of these alternative treatments with maximum statistical power by combining all direct and indirect comparisons.
- The individual participant data meta-analysis enables exploration of individual characteristics as prognostic factors and effect moderators of these alternative treatments.
- The study will contribute to differential therapeutics that match treatments to specific subgroups of patients and thereby maximise the overall response rates among patients with persistent depressive disorders.
- The IPD-NMA will not be able to examine variables that have not been measured in the original studies.

INTRODUCTION

Chronic depression has an estimated lifetime prevalence from 3% to 6%[1 2] and subsumes several clinical subtypes including chronic major depression, recurrent major depression with incomplete inter-episode recovery and chronic minor depression (dysthymia). When examined among themselves, few clinical or psychosocial differences emerged between the subtypes,[3 4] and they are now categorised together as persistent depressive disorder in Diagnostic and Statistical Manual Fifth Edition (DSM-5). When compared with acute forms of depression, chronic depression is characterised by greater comorbidity, greater social dysfunction, impaired physical health and more frequent suicide attempts and hospitalisations.[5]

Despite the prominent personal and societal burden of persistent depressive disorder, it is often underrecognised and undertreated.[6] Important advances in psychological and pharmacological treatments have been made in the past decades but, on average, the responses to these treatments remain typically slow and poor.[7] Differential responses among different modalities of treatments or their combinations remain poorly understood, and different systematic reviews including a network meta-analysis conclude with different recommendations.[8–11]

This confusion may be partly due to lumping different forms of psychotherapies into one class. In this study, we will therefore focus on the one psychotherapy that has been specifically designed for chronic depression, the Cognitive-Behavioural Analysis System of Psychotherapy (CBASP).[12] It is a highly structured psychotherapy integrating behavioural, cognitive and mainly interpersonal treatment strategies. Its main therapy target is learning to recognise the consequences of one's own behaviour on other persons, to develop social problem-solving skills and to generate authentic empathy. It has been examined against medications, alone or in combination and against other psychotherapies, in an increasing number of trials.

The confusion may also be partly due to failure to account for the impact of important patient characteristics that might modify treatment effect. Increasing attention has been given to personalised medicine[13] and, more recently, precision medicine.[14] This is relevant when several alternative treatments are available and the differences in their effectiveness are, on average, small; in such cases, a more differentiated approach that matches treatments to specific subgroups of patients might increase the overall response rate.[15 16] Albeit a catchy phrase, 'personalised medicine' is probably a misnomer because medicine can never be personalised in the sense of recommending a particular treatment to a particular individual, but can only specify ever finer smaller groups of individuals for whom one of the many alternative treatments is expected to be more effective than the others. We therefore prefer to use the term 'differential therapeutics' to refer to this approach. From this perspective, heterogeneity in treatment effects is a boon. Factors that have an impact on the relative treatment effect thus causing heterogeneity are called effect moderators or effect modifiers. Methods are rapidly developing to enable discovery of prognostic factors (variables that predict overall response regardless of the treatments) and effect modifiers (variables that predict differential response to alternative treatments).[17–20] One promising approach is to apply meta-regression to the network meta-analysis of individual participant data (IPD-NMA), which would enable more powerful examination of the influence of both group-level and individual-level characteristics on the outcomes in the comparison of three or more alternative treatments.[21]

This study therefore aims to conduct an IPD-NMA of CBASP, pharmacotherapy and their combination, to identify their prognostic factors and effect moderators, and to propose differential therapeutics in the treatment of chronic depression.

METHODS

Criteria for considering studies for this review

We will search for all randomised controlled trials that compared any two of CBASP, pharmacotherapy, or their combination, in the treatment of patients with chronic depression. No language limitation will be employed.

Participants

Participants will include men or women, aged 18 years or older, who suffer from chronic depression. Chronic depression includes persistent depressive disorder (DSM-5), dysthymic disorder, or chronic major depression or recurrent major depression, with incomplete interepisode recovery (DSM-4), or any corresponding conditions according to standard operationalised diagnostic criteria.

A concurrent secondary diagnosis of another psychiatric disorder will not be considered as an 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.

Interventions

Participants must be allocated to one, in comparison with another, of the following three treatments:

1. CBASP;
2. Antidepressant pharmacotherapy, which could include any of the antidepressive agents licensed for the treatment of major depression in the country where the trial was conducted;[22]
3. Their combination.

Search methods for identification of the studies

We will first conduct an electronic search of Cochrane CENTRAL, PUBMED, SCOPUS and PsycINFO, with the keywords: CBASP or 'Cognitive-Behavioral Analysis System of Psychotherapy' and Depressive disorder.

CBASP is a relatively new psychotherapy, specifically developed for chronic depression, by James P McCullough Jr, PhD, and the training programme has been supervised by its developer since the early days (http://www.cbasp.org). We will therefore conduct a supplementary search for any additional relevant trials through personal contact with Professor McCullough.

The list of the identified trials will then be sent out to each study's principal investigators to ask for further possibly relevant trials.

Data collection and management

Individual participant data including the dependent as well as independent variables as specified below will be sought from the principal investigators of all the identified trials. Since the same or similar constructs may be measured with different scales in each of the included studies and different reports from the same study will be reporting on different aspects of the conducted study, we will also obtain their study protocols and the administered rating scales.

The veracity of the obtained data will be cross-examined by calculating the summary statistics (numbers and percentages, or means and SDs) of the baseline demographic as well as clinical variables, and comparing them against the published reports.

Measures

Dependent variables

Our primary outcomes will be:

1. Depression severity as measured on a continuous observer-rated scale for depression. Where different scales such as Montgomery-Asberg Depression Rating Scale (MADRS) or different versions of Hamilton Rating Scale for Depression (HAM-D) are reported, we will attempt to transform them into the 24-item HAM-D, using the conversion table based on the item response theory[23] (http://www.ids-qids.org/idsqids.pdf). When repeated measures are available, we will incorporate them into the analyses.
2. Dropouts for any reason, as a proxy measure of overall treatment acceptability.

As secondary outcomes we will use:

1. Treatment response, defined as 50% or greater reduction from baseline to study end point in the study's primary observer-rated depression scale
2. Remission, defined as scoring below the following validated thresholds at end point: 7 or less on 17-item HAM-D[24] or 10 or less on MADRS.[25]
3. Depression severity as measured on a continuous self-rating scale for depression, such as Beck Depression Inventory (BDI) or Inventory of Depressive Symptomatology, Self-Report. Different scales will be converted into BDI using the conversion table of self-rating depression scales[26] (http://www.ids-qids.org/idsqids.pdf).
4. Social functioning, as measured by any validated measure for global social functions such as Global Assessment of Functioning[27] or Social Adjustment Scale-Self Report.[28]

Independent variables

The literature suggests many candidates for effect predictors (variables associated with response regardless of the treatment) and for effect modifiers (variables associated with differential response depending on the treatment) in the treatment of depression.[29] We have listed the possible candidate variables for effect predictors and effect modifiers based on the literature in the following.

However, we will select the limited number of variables to be entered into our analyses when they are particularly pertinent in the differential treatment of chronic depression in the context of psychological and pharmacological treatments. The variables will first be limited by their availability in the included original studies, but when several variables that measure similar things are available, the research team will discuss those we believe are the most important predictors and those that should be included in the model. We will also examine this limited set of variables in the meta-regression for the primary outcomes only.

Demographics

1. Age[30]

Life and social history

2. Childhood maltreatment[31]
3. Education[32]
4. Employment[16 33]
5. Marital status[15 16 33]
6. Recent life events and difficulties[16 33]
7. Social adjustment/function[34]

History of present illness

8. Age at onset[35]
9. Chronicity[30]
10. Number of previous episodes[32 36]
11. Prior treatments with antidepressants[16]
12. Prior treatments with psychotherapies

Present illness: symptomatology

13. Subtype of chronic depression (chronic major depression, recurrent major depression with incomplete interepisode recovery, dysthymia)
14. Baseline severity[37–39]
15. Baseline psychomotor symptoms[34 40]
16. Baseline anxiety symptoms[40 41]
17. Baseline somatic anxiety[34]
18. Comorbid personality disorder[16]
19. Comorbid substance use/abuse[40]

Therapeutic process

20. Patient preference[42 43]
21. Therapeutic alliance[44 45]
22. Early response[46]
23. Co-prescriptions other than antidepressants

Assessment of risk of bias

We will assess risk of bias in the included studies, using the tool described in the Cochrane Collaboration Handbook as a reference guide.[47] The assessment will be carried out by two independent raters. If the raters disagree, the final rating will be made by consensus with the involvement (if necessary) of another member of the review group. We will evaluate the risk of bias in the following domains: generation of allocation sequence, allocation concealment, blinding of study personnel and participants, blinding of outcome assessor, attrition, selective outcome reporting and other domains including sponsorship bias.

Where inadequate details of allocation concealment and other characteristics of trials are provided, the trial authors will be contacted in order to obtain further information. We will not include studies where sequence generation was at high risk of bias and where allocation was clearly not concealed.

Publication bias

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.

Analyses

We will synthesise data using a one-step IPD meta-analysis model assuming independent interaction between treatment effects and covariates, as described by Donegan *et al*[50] (model 2). We will 'borrow strength' across the multiple time points by assuming that the observations from each patient follow a multivariate normal distribution, thus accounting for the correlation between the observations. Then, for study j comparing treatments X and Y, for the observations at the study's end point we will assume that:

$$m_{ijX} = u_j + \alpha_j x_{ij}, \text{ if patient i received treatment X}$$
$$m_{ijY} = u_j + \alpha_j x_{ij} + (\beta_{DX} - \beta_{DY})(x_{ij} - \bar{x}) + \delta_{jYX} + \mu_{DX} - \mu_{DY}, \text{ if patient i received Y}$$

where X is the (arbitrarily chosen) reference treatment for study j, $\delta_j \sim N(0,\tau^2)$, τ^2 is the heterogeneity (common for all comparisons), x_{ij} is a covariate, and the coefficients β measure the interaction between the relative treatment effects and the covariate values. The coefficients α_j measure the impact of the covariate on the end point outcome that is irrespective of the treatment being taken. The model described above pertains to both continuous and dichotomous outcomes. The latter will be assumed to follow a Bernoulli distribution, where m_{ijk} (k=X,Y) will correspond to log-odds.

We will opt for IPD data from all included studies; however, if there are studies for which only aggregated data are available, we will include those as described in Donegan *et al* by distinguishing within-trial and between-trials interactions (model 5). If a trial is identified that compares all three interventions, we will substitute the random-effects distribution of δ_j for its bivariate distribution.

The model will be fitted in OpenBUGS, using vague priors for all location parameters (effect sizes and regression coefficients). For the heterogeneity, we will use a half-normal prior on the SD. We will use the select variables from the above list as regressors.

Missing data

We will impute missing data in OpenBUGS, assuming a missing at random (MAR) missingness mechanism.[51] In order to test robustness of this assumption, we will run a sensitivity analysis in which we will estimate effect sizes, assuming that the missing data are not missing at random, and we will employ expert opinion about variables associated with informative missing.

Estimation of heterogeneity and inconsistency

We expect that heterogeneity and inconsistency introduced by variability in patient characteristics will be accounted for by the meta-regression model. Residual heterogeneity in the data will be measured by monitoring the common heterogeneity parameter τ^2 and by comparing it to its empirical distribution.[52 53] Residual inconsistency will be assessed by estimating the difference w between direct and indirect estimates in the drug-psychotherapy-combination loop of evidence. This will be achieved by adding w in the equation for m_{ijP}, for studies comparing psychotherapy and combination therapy.

DISCUSSION

We have presented the study protocol for an individual participant data network meta-analysis of CBASP, antidepressant pharmacotherapy or their combination in the treatment of persistent depressive disorder.

Possible limitations of this study protocol include the following. First, 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. Second, 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.

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. We hope this study will elucidate not only the differences of overall average effects of these treatment alternatives but also factors that may predict and moderate the treatment responses of these treatment alternatives, and will eventually lead to material advancement in the field of precision medicine, by enabling more differentiated therapeutics for patients suffering from this chronically disabling disorder.

Author affiliations
[1]Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan
[2]Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Freiburg, Germany
[3]Department of Clinical, Neuro and Developmental Psychology, EMGO Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[4]Institute of Social and Preventive Medicine (ISPM) & Bern Institute of Primary Care (BIHAM), University of Bern, Bern, Switzerland
[5]Department of Psychology and Psychotherapy, Witten/Herdecke University, Witten, Germany
[6]Department of Psychiatry, University of Oxford, Oxford, UK
[7]Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, USA
[8]Department of Psychiatry, Weill Cornell Medical College, New York, New York, USA
[9]Department of Psychology, Stony Brook University, Stony Brook, New York, USA

Twitter Follow Andrea Cipriani at @And_Cipriani

Contributors TAF and ES conceived the study. All the authors provided input into the study design and helped write the study protocol. GS and OE were responsible for the statistical analysis plans. ES, JM, MBK, JHK and DNK contributed to the original data acquisition. ESW and PC helped with data acquisition and administration for IPD-NMA. TAF, ES and PC supervised the overall conduct of the study. All the authors read and approved the final protocol.

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Data sharing statement This is a study protocol for an individual participant data network meta-analysis. Data collected during the research will be managed by ESW and made available to the research team.

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