Original research

Cognitive-behavioral analysis system of psychotherapy (CBASP), drug, or their combination for persistent depressive disorder: Personalizing the treatment choice using individual participant data network meta-regression

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ABSTRACT

Background: Persistent depressive disorder is prevalent, disabling and often difficult to treat. Cognitive-behavioral analysis system of psychotherapy (CBASP) is the only psychotherapy specifically developed for its treatment. However, we do not know which of CBASP, antidepressant pharmacotherapy or their combination is the most efficacious and for which types of patients. This study aims to present personalized prediction models to facilitate shared decision making in treatment choices to match patients' characteristics and preferences based on individual participant data network meta-regression.

Methods: We have conducted comprehensive search for randomized controlled trials comparing any two of CBASP, pharmacotherapy or their combination and sought individual participant data from identified trials. The primary outcomes were reduction in depressive symptom severity for efficacy and dropouts due to any reason for treatment acceptability.

Results: All three identified studies (1,036 participants) were included in the present analyses. On average, the combination therapy showed significant superiority over both monotherapies in terms of efficacy and acceptability, while the latter two treatments showed essentially similar results. Baseline depression, anxiety, prior pharmacotherapy, age and depression subtypes moderated their relative efficacy, which indicated that for certain subgroups of patients either drug therapy or CBASP alone was a recommendable treatment option that is less costly, may have less adverse effects and match individual patient's preferences. An interactive web-app (https://kokoro.med.kyoto-u.ac.jp/CBASP/prediction/) shows the predicted disease course for all possible combinations of patient characteristics.

Conclusions: Individual participant data network meta-regression enables treatment recommendations based on individual patient characteristics.

INTRODUCTION

Persistent depressive disorder refers to chronic forms of depression in which the depressed mood and associated symptoms persist for two years or more [1]. Persistent depressive disorder is a major public health problem owing to its frequency and its impact. In the general population, it has an estimated lifetime prevalence of 3-6% [2]. Up to one-third of individuals with acute depression develop a chronic course [3]. When compared with acute episodic depression, persistent depression is associated with a greater rate of comorbid psychiatric disorders, greater social impairment and lower quality of life, more impaired physical health, and more frequent suicide attempts and hospitalizations [4].

The past decades have seen some important advances in the pharmacological and psychological treatments of persistent depressive disorder. Even to this date however, it is often underrecognized and undertreated [5]. When treated, patients' responses typically tend to be slow and poor with substantial residual symptoms [4]. Differential responses among the available treatments are insufficiently explored, and previous systematic reviews including network meta-analyses concluded with different recommendations [6-9].

This confusion may be partly due to lumping together different forms of psychotherapies and also to application of different methodologies of evidence synthesis. For example, older reviews included all forms of psychotherapies such as cognitive behavioral therapy or interpersonal psychotherapy and could not reach clear conclusions [8, 9]. Two more recent reviews, by contrast, examined specific forms of psychotherapies but did not meta-analytically synthesize the available studies or explore possible sources of heterogeneity and instead based their recommendations on narrative review of the identified trials [6, 7]. The only specific psychotherapy that has been tailored for chronic depression is the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) [10]. The initial trial

showed that it had comparable effects as antidepressant medication and significantly increased efficacy when combined with medication [11]. Subsequent trials have, however, shown mixed results [12, 13], and the relative efficacy of CBASP, antidepressant medication or their combination, let alone their relative indications for particular patients, is yet to be clarified. A novel study is now warranted to synthesize the available evidence and explore the sources of reported heterogeneity in treatment effects.

Providing the treatment that best fits each individual patient has always been an ideal practice in medicine [14]. One approach to this end, taken in personalized or precision medicine, is to find subgroups of patients that show differential response based on their distinctive genetic, biological or psychosocial characteristics [15]. After some pioneering work in finding subgroups for whom the average treatment effects may not apply [16], methods are now rapidly developing to explore possible sources of heterogeneity in treatment effects and to identify patient characteristics to guide differential therapeutics [17, 18].

A large body of high quality data is needed to meaningfully explore characteristics that should be accounted for when choosing an intervention. Meta-analysis offers a framework to synthesize evidence from multiple studies. When more than two treatment alternatives are available, network meta-analysis will take full advantage of the available data by comparing all treatments simultaneously and can elucidate the relative effectiveness among the competing alternatives. An increasingly large number of network meta-analyses have been published in the medical literature and in particular in mental health [19]. However, conventional meta-analysis of trial-level summary data, either pairwise or in network, cannot properly assess the impact of individual characteristics. For this we need individual participant data. Individual participant data network meta-analysis (IPD-NMA) and meta-regression (IPD-NMR) based on all relevant clinical trials enables a more powerful examination of the influence

of both individual- and group-level characteristics and can optimally guide treatment decisions among the various treatment alternatives with the highest possible precision [20, 21]. There have been several pioneering works to utilize individual participant data in the framework of pairwise or network meta-analyses in the past two decades [21, 22] and important insights into influence of individual-level characteristics have been obtained. For example, baseline severity has been demonstrated to moderate treatment response to antipsychotics in schizophrenia [23] and mania [24] (the greater the baseline severity, the larger the advantage of medication over placebo) but not for cognitive behavioral therapy for depression [25].

This study aims to conduct IPD-NMA and IPD-NMR to compare CBASP, antidepressant medication and their combination among patients with persistent depressive disorder. The goal is to provide the tools that will enable differentiated, fine-tuned and informed treatment choices for the patients, their families and their clinicians.

METHODS

This systematic review has been registered in PROSPERO (registration number CRD42016035886) and its full protocol has been published [26]. The reporting follows the PRISMA extension guideline for NMA [27].

Selection criteria and search strategy

We sought all randomized controlled studies that compared any two of CBASP, antidepressant pharmacotherapy, or their combination in the treatment of patients with PDD.

Participants had to be men or women, aged 18 or older, with persistent depressive disorder (DSM-5), chronic major depression, recurrent major depression with incomplete interepisode recovery or dysthymia (DSM-IV), or any corresponding conditions according to standard diagnostic criteria. Studies in which all participants had a primary medical condition or a concurrent primary diagnosis of another mental disorder were excluded: a concurrent secondary diagnosis of another mental disorder was not considered an exclusion criterion.

Antidepresssants could be any of the antidepressive agents licensed for the treatment of major depression in North America, Europe or Japan.

We first conducted an electronic search of Cochrane CENTRAL, PubMed, Scopus and PsycInfo, with the keywords: CBASP or 'Cognitive-Behavioral Analysis System of Psychotherapy' and 'Depressive disorder.' We then sent the list of the identified trials to each study's principal investigator to ask for further relevant trials. We imposed no language restriction.

Data collection and assessment of risk of bias

We requested the principal investigators of the identified trials to provide us with the study protocol, assessment instruments used and individual participant data including the pre-specified dependent and independent variables (see below, Patient, treatment and trial characteristics).

We cross-examined the obtained data against the summary statistics (numbers and percentages, or means and SDs) of the baseline demographic and clinical variables as reported in the publications of each study. When the same or similar constructs were measured with different scales in the included studies, we standardized each construct according to the pre-specified rules (for details, see Table 1); once the dataset was locked, the IPD-NMA and NMR were undertaken.

Two independent raters assessed the risk of bias in the included studies using the tool described in the Cochrane Collaboration Handbook [28] as being at high risk of bias, low risk of bias or unclear 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.

Outcomes

Our primary outcomes were:

(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) were used, we transformed them into the 24-item HAM-D, using a conversion table based on the item response theory [29].

(2) Dropouts for any reason, as a proxy measure of treatment acceptability.

As deterioration on treatment is an often neglected yet clinically important outcome [30, 31], we set as a secondary outcome:

(3) Deterioration, defined as scoring above the baseline measurement on a continuous observer-rated scale for depression.

Patient, treatment and trial characteristics

We collected data on characteristics that can act as effect modifiers (EMs, variables that predict differential response to alternative treatments) and prognostic factors (PFs, variables that predict the overall course of a condition regardless of the treatments). We pre-specified the following variables to be examined based on the literature [32].

Demographics

1) Age

Life and social history

2) Childhood maltreatment (emotional or physical abuse, neglect, sexual abuse)
3) Marital status (married, single, widowed/separated/divorced)
4) Social adjustment/function, as measured with Global Assessment of Functioning [33]

History of present illness

5) Age at onset
6) Length of current episode
7) Number of previous episodes
8) Prior treatments with antidepressants
9) Prior treatments with psychotherapies

Present illness: symptomatology

10) Subtype of chronic depression (chronic major depression, recurrent major depression with incomplete interepisode recovery, dysthymia)
11) Baseline severity
12) Baseline anxiety, based on anxiety/arousal factor of IDS-SR [34]
13) Comorbid personality disorder

Statistical methods for evidence synthesis

We first synthesized data using IPD-NMA [20]. We combined information about multiple treatments and multiple outcomes measured at different time points. We developed a model that jointly synthesizes information on outcomes measured at multiple time points, while stochastically imputing missing outcome data assuming that they were missing at random. Due to the small number of identified studies per comparison,

estimating heterogeneity in a random effects model was not feasible; fixed-effects models were employed in all analyses.

Consistency refers to the statistical agreement between direct and indirect estimates in the network and is a prerequisite of network meta-analysis [35]. If consistency does not hold, network meta-analytic results may be biased. We evaluated statistical inconsistency using the design-by-treatment inconsistency model [36].

We then extended the model to an IPD-NMR by including in the model covariates that we identified as important effect modifiers or prognostic factors. To identify important covariates we fitted a penalized regression model, using the `glmnet` package in R [37]. We only included covariates that were reported in all studies, and we performed multiple imputations for sporadically missing covariates. We explored first and second order combinations of these covariates, and their interactions with the treatment. In order to pinpoint which covariates or treatment-covariate interactions to include in the model, we performed internal cross-validation. We fitted the model separately in each multiply imputed dataset, and we kept the terms that were selected by the penalized regression model in all datasets. Once a set of covariates is selected, we included them in a IPD-NMR model and we generated predictions for the disease course under each treatment regime, given a set of patient characteristics. We created an interactive web-application which accepts as inputs values for those characteristics selected as important in the model and generates the corresponding outcome predictions.

The models were fitted within a Bayesian framework using the OpenBUGS software [38] and vague priors for the relative treatment effects. Supplement 1 provides additional details of the statistical models and analyses performed.

RESULTS

Selection of included studies

The initial electronic search identified 671 references, from which six studies were identified as randomized controlled trials involving CBASP. Inquiry with the principal investigators added one completed study. Of these, three studies [11, 12, 39] compared at least two of CBASP, antidepressant pharmacotherapy, or their combination in the treatment of patients with PDD. See Figure S1 in the online Supplement for the PRISMA flow diagram.

All the investigators agreed to collaborate with the present study and provided the requested protocols, rating scales and data. The individual participant data for Kocsis et al [12] were made available through the NIMH Data Repositories.

All the three studies were rated at low risk of bias in all the assessed domains, except for blinding of participants and personnel for which all three were at high risk of bias. The ratings were unanimous between the two independent raters.

Figure 1 presents the network structure of the three included studies. Table 1 shows the baseline demographic and clinical characteristics of the participants. The patients were similar in terms of age, gender, age at onset, length of current episode or baseline social functioning. On the other hand, prior treatment differed among studies, mainly due to the study designs: in Kocsis (2009), patients were randomized to second-step pharmacotherapy with or without CBASP after they had shown no or partial response to first-step pharmacotherapy [12]. All participants therefore had had prior pharmacotherapy when they entered the randomization phase and had relatively low depression and anxiety severity upon randomization. In Schramm (2015), patients with PDD were initially randomized to CBASP or to escitalopram but after eight weeks of such acute phase treatment, responders continued with the allocated treatment while non-responders were augmented with the other treatment up to 20 weeks [39]; the data

from the initial randomized comparison was used in the present analysis, because the comparison after 8 weeks is no longer between CBASP and escitalopram per se. In the online Supplement, Table S1 tabulates data availability for depression severity by week for each study, and Figure S2 shows the pooled, aggregated raw HAM-D score changes of the participants allocated to each treatment.

Average relative treatment effects: IPD-NMA

Table 2 shows the IPD-NMA results for the two primary outcomes (depression severity and dropouts for any reason). The model accounted for correlations across time-points but did not adjust for covariates. Thus, results refer to the whole population, on average. In this analysis, combination treatment emerged as the best treatment.

Relative treatment effects for patient with specific characteristics: IPD-NMR

Table 3 shows the covariates (or combinations of covariates) which were selected as EMs and PFs for the two primary outcomes, while Tables S3 and S4 in the online Supplement provide parameter estimates for the selected covariates. The results indicate that the most influential covariate for depression severity was baseline HAM-D, which was selected both as PF and EM. Additional EMs included IDS anxiety factor and prior medication. For dropout, age and depression subtype also played a prominent role.

Table 4 and Figure 3 show the average treatment effects and dropouts within specific patient subgroups as estimated from the IPD-NMR model. As there is a large number of possible patient subgroups, in Table 4 we selected five factors (depression severity, anxiety severity, prior medication, age and depression subtype) to exemplify. The full interplay of all the identified EMs and PFs can be shown by an interactive web-app (URL: https://kokoro.med.kyoto-u.ac.jp/CBASP/prediction/, illustrated in Figure 3).

For patients with characteristics near the population averages (e.g. moderate baseline depression with moderate anxiety (Figure 3a), or low baseline depression with low anxiety) the relative treatment effects among the three arms are basically similar to the overall results shown in Table 2: the combination treatment beats both CBASP alone or antidepressants alone by about 3 or 4 points (95%CrI: approximately 2 to 6) on the 24-item HAMD, and there is no substantial difference between the latter two (Table 4). In addition the probability of dropping from treatment is estimated to be especially high (often >50%) when patients are young and suffering from chronic major depression; for other patients, the dropout probability estimates remain within expected ranges and may not cause concern for choosing treatments.

For patients with severe depression and anxiety (e.g. high baseline depression with high anxiety (Figure 3b), or moderate baseline depression with high anxiety), the advantage of the combination treatment grows, beating the antidepressant alone by around 4-5 points (95%CrI: approximately 0 to 8), which then beats CBASP alone by another 4-5 points (95%CrI: approximately -1 to 12) on 24-item HAMD (Table 4). However, the dropouts remain high both on the combination treatment and CBASP alone (>50%) when the patient is young and has chronic major depression.

For patients with moderate baseline depression but with low anxiety (Figure 3c), the relative treatment effects among the three alternative treatments change: both CBASP and the combination treatment beats the antidepressant alone treatment by 3-4 points (95%CrI: approximately 0 to 7), and there is no substantial difference between the former two (Table 4). For young patients with chronic major depression, the dropout rate on CBASP is extremely high (>70%).

We also examined EMs and PFs to identify patients for whom the treatment was detrimental. While several factors in common with those for improvement were

identified in variable selection, no strong evidence of effect modification was detected (Supplement 3, Tables S2 and S5).

Examination of heterogeneity and inconsistency

The design-by-treatment model provided no evidence of inconsistency. All inconsistency factors included in the model were found to be statistically non-significant. (For details, see Supplement 4)

DISCUSSION

We identified, and obtained individual participant data from, all three RCTs conducted to date comparing CBASP, antidepressant pharmacotherapy or their combination for the treatment of persistent depressive disorder (n=1,036). IPD-NMA revealed robust superiority, on average, of the combination treatment over CBASP alone or pharmacotherapy alone in terms of both efficacy and acceptability (approximately 3-point greater reduction on 24-item HAMD or close to 40% less odds of dropping out) and no substantive difference between CBASP alone or pharmacotherapy alone.

However, IPD-NMR allowed us to identify several potent EMs and PFs to define subgroups of patients for whom these average results would not apply. For example, patients with severe depression and severe anxiety would show symptom reduction in the distinctively descending order of the combination, pharmacotherapy and CBASP (combination is best) but dropouts from treatment in the clear ascending order of pharmacotherapy, combination and CBASP (pharmacotherapy is best), for example for young patients with chronic major depression; in such cases, pharmacotherapy may be a preferred option because the expected dropout on the combination therapy is extremely high. By contrast, patients with moderate depression and mild anxiety would benefit

equally well from the combination and CBASP alone but less from medication alone; here CBASP alone may be a preferred choice, as it is equally efficacious, less costly and may match the patient's preference.

The magnitude of difference between treatment groups and especially for specific subgroups was not only statistically significant but clinically meaningful. The minimally important change, i.e. the minimum within-person change in disease severity that patients would perceive as beneficial, has been found to be 3-5 points in the HAM-D [44, 45]. The average between-group difference between the combination therapy and either monotherapy was approximately three points and is likely to be clinically meaningful (Table 2); for some subgroups of patients, the between-group difference may reach nine points and is definitively clinically important (Table 4).

The finding that some patients may not require drugs is clinically important because this will help them avoid unnecessary side effects including eventual withdrawal effects and iatrogenic aspects associated with long-term antidepressant treatment [31, 46, 47].The finding that some other patients may derive comparable benefits without psychotherapy is also important, as it may lead to substantial reduction in costs both in terms of time and money.

Our analyses identified the following three patient characteristics to be the most prominent EMs for efficacy estimates: baseline depression severity as measured with 24-item HAMD, baseline anxiety severity as measured with IDS anxiety factor, and prior use of medication (Table 3). Baseline depression severity has sometimes been noted as effect modifier in the choice of treatments with psychotherapy, pharmacotherapy or their combination [48, 49] but not always [50]. Anxiety or some related characteristics have also been suggested to moderate the treatment effects in several studies [51, 52] but there are far fewer studies on the impact of anxiety in the treatment of depression. Prior drug treatment was found to be an effect modifier in another study [53]. It is to note that,

while all the included studies had recruited people with chronic depression, they differed in the proportion of those with prior exposure to pharmacotherapy. For example, in Kocsis (2009) all patients had had pharmacotherapy [12] and in Keller (2000) 60% did so [11], while in Schramm (2015) 24% of patients had had neither prior pharmacotherapy or psychotherapy [39]. This variability allowed IPD-NMR to identify prior medication history to be one of the effect modifiers. It is also important not to equate chronicity with treatment resistance in the application of the current prediction model.

Previous studies have suggested a number of other sociodemographic and clinical variables as EMs in the choice of psychotherapy or medication for the treatment of depression, including age, marital status, employment status, childhood maltreatment, recent life events, or outpatient treatment [53, 54]. We were unable to examine the effects of life events (not measured in any of the included studies) or outpatient status (all included studies were conducted with outpatients) but for the remaining variables the effect was less pronounced and they were therefore not included in our final models.

Of particular note, childhood maltreatment was not included as an EM but only as PF in our models. A systematic review has shown that childhood maltreatment can be both PF for overall poor prognosis and EM in the choice of pharmacotherapy or psychotherapy in depression treatments [55]. Previously, a secondary analysis from Keller (2000) indicated that among patients without childhood trauma, the descending order of efficacy of treatment was combination, pharmacotherapy and CBASP, while among those with childhood trauma, it was the combination, CBASP and pharmacotherapy [56]. They concluded that CBASP was an essential element in the treatment of patients with persistent depressive disorder and a history of childhood trauma. When we combined all relevant data and conducted IPD-NMR, physical or emotional neglect emerged as an important PF but was not included in the models as an EM. There may be several reasons for this apparent discrepancy between their findings and the current results.

First, the three studies contributing to the current IPD-NMR measured childhood maltreatment with different measures (See Table 1), which may have influenced the relationship between childhood trauma and the treatment effects in an unmeasurable way. Second, the statistical analyses were different between theirs and our study. They applied the general linear model to the completers' data while specifically focusing on the influence of childhood maltreatment. Our aim, however, was not to examine whether childhood maltreatment had statistically significant effect on the relative effects but to build the best predictive model.

Our analysis identified several factors that may act as EMs and PFs to predict deterioration on treatment. However, the models overall were unable to detect strong effect modification. This was perhaps due to the small number of subjects who scored worse than their baseline in our dataset: only some 10% of the patients showed deterioration after treatment. In the future, when we have assembled larger datasets, the current methodology can be expected to provide important insights in identifying participants likely to deteriorate on pharmacotherapy or psychotherapy [30, 31].

There are several weaknesses to our study. The biggest limitation, common to any re-analyses of available data, was that we were able to analyze only what was made available to us. Some studies did not measure the outcomes important to our hypotheses (e.g. recent life events) or measured them differently (e.g. childhood maltreatment). We conceptualized childhood maltreatment as presence/absence of abuse, neglect and sexual abuses to both be consistent and retain as much information as possible across all the included studies. Secondly, we limited ourselves to CBASP, the only psychotherapy specifically developed for chronic depression, and thus do not know if the current findings apply to other psychotherapies in the treatment of chronic or other depressions. This specificity of our study, however, is also a strength: our current findings are clinically pertinent when we consider the treatment of persistent depressive disorder with CBASP.

Thirdly, while focusing on CBASP, the included participants and the employed antidepressants were heterogeneous. Medications were different among the three included studies (nefazodone, escitalopram, and various other new generation antidepressants). Nefazodone, that was used in the largest of the three trials [11], was withdrawn from the market for hepatotoxicity. The populations were variable, including those with established antidepressant resistance to those naïve to pharmacotherapy or psychotherapy. There was, however, no substantive inconsistency in the network and this variability allowed us to explore subgroup differences in the response to three alternative treatments. Similar analyses are warranted in the future for more studies employing other types of antidepressants and other types of psychotherapies in order to further guide their individualized treatments. Cross-methodological data synthesis from experimental and observational studies including one-arm clinical trials, cohort data and data from registries is an emerging area of research that can bridge the gap between evidence from well-controlled randomized trials in selected patient groups and real-world evidence [57, 58].

It is to note that the statistical methods employed in our analysis did not break the internal comparisons of the studies. Both pairwise and network meta-analyses preserve the randomization of the studies [59]. From each study a relative treatment effect is calculated separately at the first level (respecting randomization) and then study-specific effects are synthesized at the second level. In this way, patients in one trial are not directly compared with patients in another trial. The use of regression at the IPD-level and subgroup analyses equally preserve randomization. Indirect comparison in NMA makes inferences about treatments which have not been directly compared. Although NMA and meta-regression do respect the within-study randomization, the evidence they provide can be viewed as non-randomized because the treatment comparisons have not been randomized across the studies [60].

By contrast the strengths of our study may be summarized as follows. First, we were able to identify and include all the individual participant data from the relevant RCTs, which enabled us to conduct publication-bias-free re-analyses to make individual predictions. The study is free from data availability bias often seen in individual participant data analyses to date [61]. Second, the available data constituted a triangular network of the three major competing treatments, to which we applied the network meta-regression so that we were able to gain more power by combining direct and indirect comparisons, as compared to an ordinary, pairwise meta-analyses. There was no detectable inconsistency in the included studies and we were able to make more precise effect estimates than in the original studies. Third, the rich IPD enabled us to apply the same imputation approach for missing data consistently across the included studies, while fully taking into account the repeated measurements in the studies. Fourth, our analyses are more advanced than several previous attempts to synthesize the knowledge of the identified EMs and PFs in making individual predictions of treatment effects [62, 63], because (i) we provide individual predictions simultaneously for more than two treatments, (ii) we model both efficacy and acceptability of the treatments, (iii) we use internal cross-validation of single- and second-order EMs and PFs. The last feature has rarely been realized in the personalized treatment prediction models so far because all too often a sample size from a single study is relatively small [62], although it has been repeatedly pointed out that using the whole dataset as the derivation set risks overfitting the model to the dataset and producing spurious and non-replicable findings when building a prediction model [63, 64]. However, the true test of our model would call for an external validation study, ideally a randomized trial that incorporates the stratifications we have identified. Lastly, the resulting individualized prediction model allows for each patient's values and preferences to play greater roles and some individuals to rightly opt for psychotherapy alone or pharmacotherapy alone.

Such optimized and individualized decision making would not only lead to greater patient satisfaction but also substantial reduction in costs including time, money, efforts and/or side effects.

In conclusion, the present study represents the first attempt to build a personalized prediction model to facilitate shared decision making when patients and their clinicians discuss their treatment for persistent depressive disorder. We would encourage use of our interactive web application (https://kokoro.med.kyoto-u.ac.jp/CBASP/prediction/) when clinicians and patients discuss their options and choose the treatment that is most likely to bring about the desired outcomes, taking into account each patient's individual characteristic such as age, baseline depression severity, baseline anxiety severity etc. The methodological implications of the current and similar studies may be far-reaching: days are probably gone when the blanket treatment recommendations based on group average were the best we could provide to our patients. We hope to see development of similar interactive tools when viable alternative treatments exist for the same indication through collaborative sharing of individual clinical trial data. Ideally such efforts should share the common protocols so that data can be synthesized more easily and more consistently across accumulating evidence [65].

Author Contributions

TAF, OE and ESW had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. TAF, OE, GS and ES conceived the study and developed the study plan. TAF, ESW, MBK, JHK, DNK, JM and ES acquired and managed the data. OE and GS analyzed the data. TAF, OE, ESW, AC, MBK, JHK, DNK, JM, GS, PC and ES interpreted the data. TAF and OE drafted the manuscript and all authors made substantial revision to earlier drafts and approved the final manuscript.

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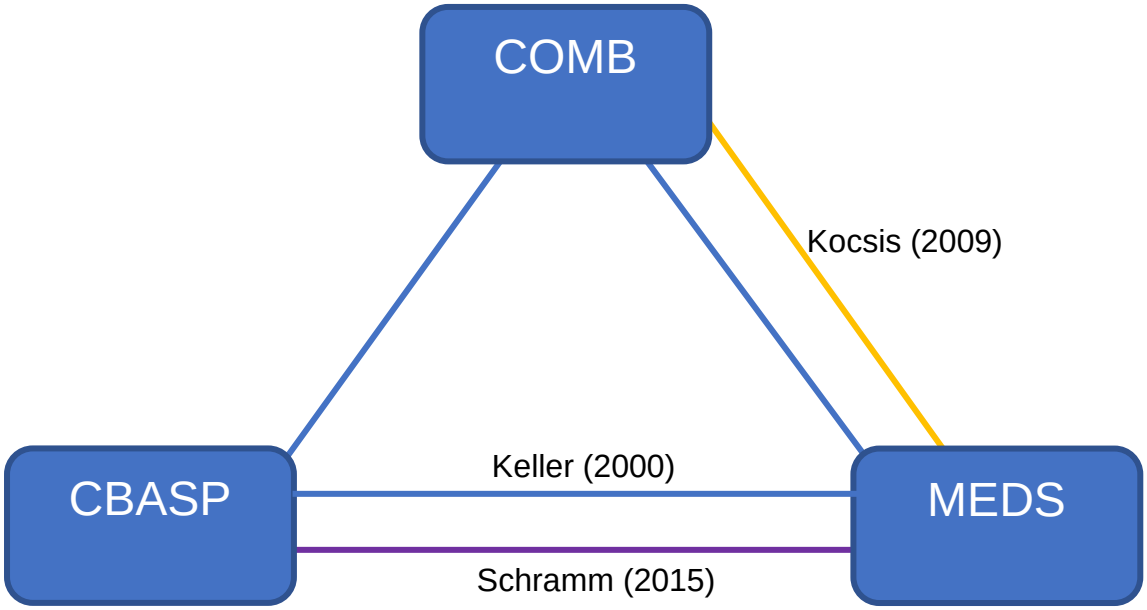
Figure 1. Network structure

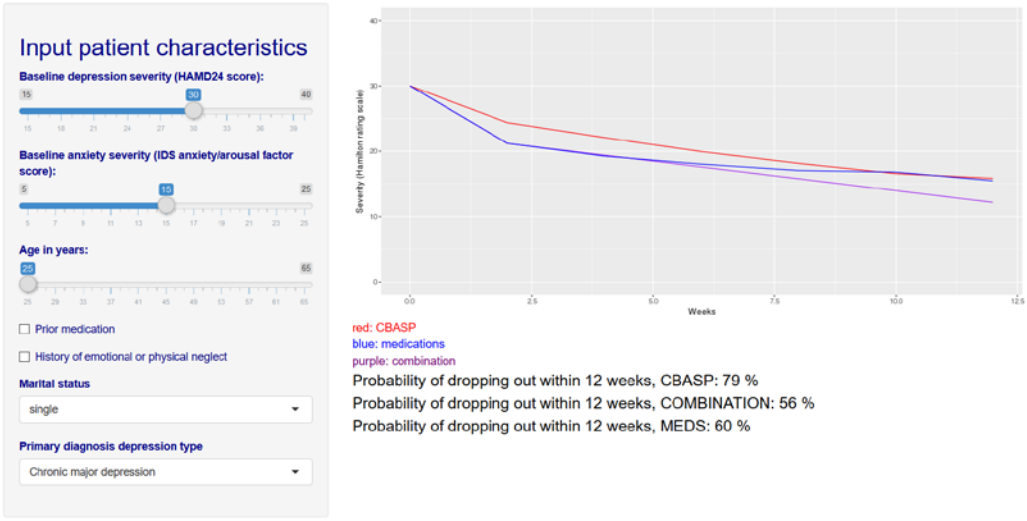


CBASP: Cognitive-Behavioral Analysis System of Psychotherapy
MEDS: Antidepressants
COMB: Cognitive-Behavioral Analysis System of Psychotherapy + Antidepressants

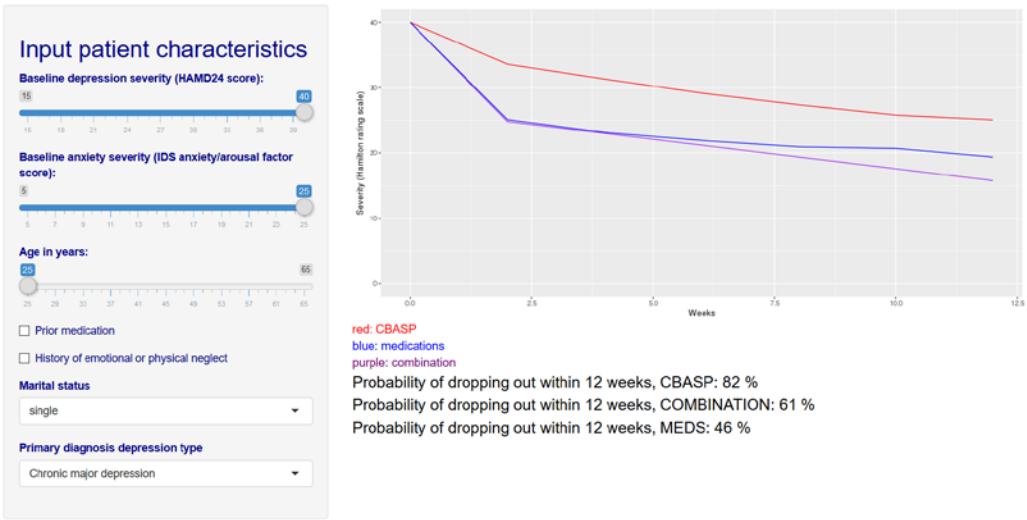
Keller (2000) [11]
Kocsis (2009) [12]
Schramm (2015) [39]

Figure 2. Interactive webpage for individual prediction of depression severity and risk to dropout (https://kokoro.med.kyoto-u.ac.jp/CBASP/prediction/)

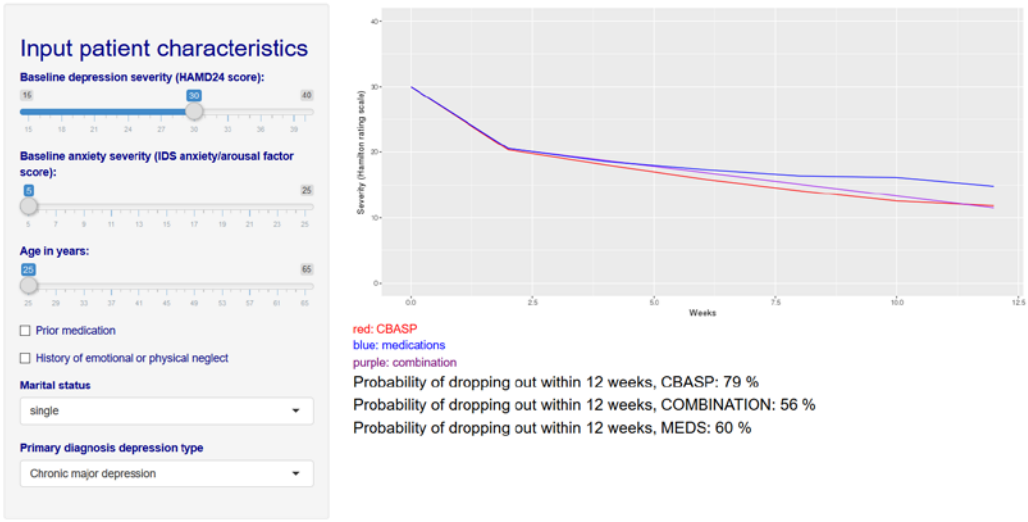
2a Patients with moderate baseline depression and moderate anxiety*



2b. Patients with high baseline depression and high anxiety*



2c. Patients with moderate baseline depression and low anxiety*



* The other effect modifiers and prognostic factors were set to: Age=25, Prior medication=No, History of emotional or physical abuse=No, Marital status=Single, and Primary diagnosis depression subtype=Chronic major depression.
† For people who cannot access the website, the same functionality provided on Excel sheet is available from the corresponding author upon request.

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Table 1. Baseline demographic and clinical characteristics of the patients in the included studies

Variables	Keller (2000) [11]		Kocsis (2009) [12]		Schramm (2015) [39]	
Number of randomized patients	228 to CBASP 226 to MEDS 227 to COMB		96 to MEDS 200 to COMB		29 to CBASP 30 to MEDS	
Medications used	nefazodone		sertraline, escitalopram, bupropion, venlafaxine, mirtazapine		escitalopram	
	Mean	SD	Mean	SD	Mean	SD
Age, mean (SD)	43.3	10.7	45.1	12.5	43.6	10.6
Education (yr)	-		15.4	3.1	11.6	1.8
Age at onset	26.8	13.1	26.2	12.8	-	
Length of current episode (wk)	407	497	367	459	-	
Baseline depression severity (24-item HAM-D)	26.9	5.0	19.2	8.2	26.2*	9.2
Baseline anxiety severity (IDS anxiety factor)	13.8	4.6	8.6	4.9	14.4	4.9
Baseline functioning (Global assessment of functioning)	53.8	5.6	53.8	8.1	53.8	11.7
	N	%	N	%	N	%
Female sex (%)	445	65.3	159	53.7	32	54.2
Employed	-		176	60.0	39	70.0
Married	291	42.7	202	41.2	19	33.9
Depression diagnosis						
Chronic MDD	239	35.1	110	37.2	9	15.3
Recurrent MDD without remission	154	22.6	88	29.7	13	22.0
Dysthymia	288	42.3	98	33.1	37	62.7
Prior use of medication	410	60.2	296	100	34	57.6
Prior use of psychotherapy	444	65.2	0	0	40	67.8
Personality disorder	240	35.3	-		24	40.7
History of abuse						
Abuse	131**	19.4	39†	16.7	28‡	47.5
Neglect	27**	4.0	43†	18.4	35‡	59.3
Sexual abuse	111**	16.5	26†	10.9	9 ‡	15.3

MDD: major depressive disorder
HAM-D: 24-item Hamilton Rating Scale for Depression
IDS: Inventory of Depressive Symptomatology Self-Report
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* Converted from Montgomery-Asberg Depression Rating Scale into 24-item HAM-D, using the conversion table based on the item response theory [29]

** Keller (2000) [11] used Childhood Trauma Scale [40] and dichotomized them as presence/absence of abuse, neglect and sexual abuse.
† Kocsis (2009) [12] used Measure of Parental Style [41]. MOPS provides Maternal abuse and Paternal abuse scores, based on 5 items, each rated between 0=Not true at all and 3=extremely true. Abuse was judged present if either Maternal or Paternal abuse score was >10. MOPS Maternal indifference and Paternal indifference scores are based on 6 items. Neglect was judged present if either Maternal or Paternal indifference score was >12. Sexual abuse was judged present if MOPS Sexual abuse score >10. [41]
‡ Schramm (2015) [39] used Childhood Trauma Questionnaire [42]. CTQ provides Emotional abuse and Physical abuse scores. If either was in the range "Moderate to severe" or "Severe to extreme", Abuse was judged present. CTQ provides Emotional neglect and Physical neglect scores. If either was in the range "Moderate to severe" or "Severe to extreme", Neglect was judged present. CTQ provides Sexual abuse score. If it was in the range "Moderate to severe" or "Severe to extreme", Sexual abuse was judged present. [43]

Table 2. Average relative treatment effects for depression severity (in terms of points improvement on the HAM-D) and dropout for any reason

Primary outcomes	**CBASP vs COMB**	**CBASP vs MEDS**	**MEDS vs COMB**
Mean difference in depression severity at 12 weeks	2.9 (1.3 to 4.6)	0.1 (-1.6 to 1.7)	2.9 (1.6 to 4.3)
Odds ratio for dropout for any reason at 12 weeks	1.57 (1.03 to 2.28)	0.97 (0.66 to 1.41)	1.59 (1.11 to 2.27)

A mean difference larger than zero for A vs B means that patients in A have higher depression scores on average than those in B (B is a more efficacious treatment).
An odds ratio larger than one for A vs B means that patients in A have larger odds for dropouts (B is a more acceptable treatment).

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Table 3. Selected prognostic factors (PFs) and effect modifiers (EFs) for change in depression severity and dropout for any reason

Primary outcomes	**Prognostic factors**	**Effect modifiers**	
		CBASP vs COMB	**MEDS vs COMB**
Depression severity	1. IDS anxiety factor 2. HAM-D 3. Prior medication 4. $(HAM\text{-}D)^2$ 5. Neglect × HAM-D 6. HAM-D × Prior medication 7. IDS anxiety factor × Prior medication	1. $(HAM\text{-}D)^2$ 2. HAM-D × IDS anxiety factor	1. HAM-D 2. HAM-D × Prior medication
Dropout for any reason	1. HAM-D 2. Age 3. Prior medication 4. $(HAM\text{-}D)^2$ 5. $(Age)^2$ 6. Chronic MDD × HAM-D 7. Dysthymia × HAM-D 8. Age × Marital status single 9. Age × Chronic MDD 10. Marital status married ×Prior medication	1. $(Age)^2$ 2. Age × Chronic MDD	1. $(HAM\text{-}D)^2$ 2. Age × HAM-D

IDS anxiety factor: Anxiety/arousal factor score of Inventory of Depressive Symptomatology Self-Report at baseline (continuous)
HAM-D: 24-item Hamilton Rating Scale for Depression score at baseline (continuous)
Prior medication: Prior treatments with antidepressants (dichotomous)
Neglect: Emotional or physical neglect (dichotomous)
Chronic MDD: Chronic major depression (dichotomous)
Dysthymia: Dysthymic disorder (dichotomous)
Marital status married: married/de facto/in a relationship (dichotomous)

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Table 4. Average differences in HAM-D score at 12 weeks and dropout rates for the three treatments by patient characteristics

			Predicted differences in HAM-D scores at 12 weeks				Predicted dropout rates for any reason (%)					
Assumed baseline HAM-D score	**Assumed baseline IDS anxiety score**	**Prior medication**	CBASP vs COMB	CBASP vs MEDS	MEDS vs COMB	**Chronic depression subtype**	**Patient age=25**			**Patient age=60**		
							CBASP	COMB	MEDS	CBASP	COMB	MEDS
High (40)	High (25)	+	9.4 (4.5, 14.3)	4.2 (-0.8, 9.1)	5.3 (3.0, 7.6)	Chronic MDD	81	60	44	6	19	21
						Dysthymia	42	51	36	24	25	27
		-		5.9 (0.1, 11.7	3.5 (-0.3, 7.3)	Recurrent MDD	20	26	16	10	10	11
	Moderate (15)	+	2.6 (-1.2, 6.5)	-2.7 (-6.5, 1.1)	5.3 (3.0, 7.6)	Chronic MDD	81	60	44	6	19	21
						Dysthymia	42	51	36	24	25	27
		-		-1.0 (-5.8, 4.0)	3.5 (-0.3, 7.3)	Recurrent MDD	20	26	16	10	11	11
Moderate (30)	High (25)	+	7.0 (4.1, 10.1)	2.9 (-0.2, 6.0)	4.1 (2.6, 5.7)	Chronic MDD	77	54	58	5	16	24
						Dysthymia	36	45	50	19	21	31
		-		3.8 (0.4, 7.3)	3.3 (1.2, 5.3)	Recurrent MDD	25	32	36	12	13	21
	Moderate (15)	+	3.7 (2, 5.3)	-0.5 (-2.3, 1.3)	4.1 (2.6, 5.7)	Chronic MDD	77	54	58	5	16	24
						Dysthymia	36	45	50	19	21	31
		-		0.4 (-1.8, 2.6)	3.3 (1.2, 5.3)	Recurrent MDD	25	32	36	12	13	21
	Low (5)	+	0.2 (-2.6, 3.1)	-3.9 (-6.8, -0.9)	4.1 (2.6, 5.7)	Chronic MDD	77	54	58	5	16	24
						Chronic MDD	77	54	58	5	16	24
		-		-3.0 (-6.3, 0.2)	3.3 (1.2, 5.3)	Recurrent MDD	25	32	36	12	13	21

Low (20)	Low (5)	+	3.3 (1.7, 5.0)	0.4 (-1.5, 2.1)	3.0 (1.6, 4.4)	Chronic MDD	67	41	55	3	10	17
		-				Chronic MDD	67	41	55	3	10	17
						Recurrent MDD	25	32	46	12	13	21

95% Credible Intervals of predicted differences in HAM-D scores are shown in parentheses.

The other effect modifiers and prognostic factors were set to: History of emotional or physical abuse=No, and Marital status=Single.

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