General Hospital Psychiatry 61 (2019) 104–110

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

# Predicting optimal interventions for clinical depression: Moderators of outcomes in a positive psychological intervention vs. cognitive-behavioral therapy

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ARTICLE INFO

*Keywords:*
Personalized Advantage Index
Positive psychology
Psychotherapy
Cognitive-behavioral therapy
Depression
Moderators
Positive psychotherapy

ABSTRACT

Identifying differences in the clinical response to specific interventions is an important challenge in the field of Clinical Psychology. This is especially true in the treatment of depression where many treatments appear to have comparable outcomes. In a controlled trial, we compared a positive psychology group intervention, the Integrative Positive Psychological Intervention for Depression (IPPI-D; n = 62) to a cognitive-behavioral therapy group intervention (CBT; n = 66) for depression. No statistically or clinically-significant differences between the treatments were found, but a slight advantage was observed, on average, for IPPI-D. The aim of the present study was to identify and combine moderators of the differential efficacy of these two psychological interventions for clinical depression. For this purpose, a secondary analysis using the Personalized Advantage Index (PAI) was performed to identify the intervention predicted to produce the better outcome for each patient. Six of the 21 potential moderators were found to predict differential efficacy between the treatments. IPPI-D was predicted to be the optimal treatment for 73% of the sample. Baseline features that characterized these individuals were: mental and physical comorbidity, prior antidepressant medication, higher levels of negative thoughts, and higher personal growth. The 27% who were predicted to achieve better outcomes in CBT than in IPPI-D tended to have these baseline features: no comorbidities, no prior antidepressant medication, lower levels of negative thoughts, and lower personal growth.

## 1. Introduction

In 1967, Gordon Paul [1] proposed that the appropriate question to be answered by psychotherapy outcome research was "What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?" In the biomedical field, the precision medicine framework similarly aims at tailoring treatment strategies to an individual's characteristics and circumstances. Following this framework, baseline characteristics of individuals have started to be used as predictive factors of differential response to intervention strategies [2]. This information can help to develop treatment selection tools to choose the optimal treatment for each individual. The current study explored and combined moderators of outcomes in a cognitive-behavioral therapy group intervention (CBT) vs. a positive psychology group intervention (the Integrative Positive Psychological Intervention for Depression; IPPI-D).

### 1.1. Treatment selection in mental health

Diverse types of psychotherapy have shown similar efficacy for major depression, including CBT, interpersonal therapy (IPT), and problem-solving therapy (PST [3]). Although multiple treatments are available, around 38% of patients continue to meet criteria for major depression disorder (MDD) after psychotherapy. One avenue towards attempting to improve outcomes in depression is the development of new psychotherapeutic interventions that may fit better to specific

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https://doi.org/10.1016/j.genhosppsych.2019.07.004
Received 12 February 2019; Received in revised form 2 July 2019; Accepted 8 July 2019

subgroups of patients than existing ones as well as interventions that target mechanisms that were ignored by prior research.

Positive psychology interventions (PPI) have been developed to increase positive affectivity and related variables which have been downplayed in existing depression treatments, and these types of interventions may be more effective for some individuals (e.g., those low on positive affect, depressed patients with chronic anhedonia). Meta-analyses focused on the efficacy of PPI, in both clinical and nonclinical samples, have shown it is efficacious in reducing symptoms of depression as well as increasing well-being [4–6]. However, there is no evidence that PPI are superior to existing treatments [7,8], which is consistent with the general observation that when new treatments for depression are developed they are generally not more efficacious than existing alternatives [9]. This fact, along with the heterogeneity of symptoms and causes of depression [10], explains why personalizing treatments of depression is one of the major challenges, and promises, for mental health research [11]. It is believed that the lack of differences between treatments, on average, may obscure different patterns of efficacy between different types of individuals [12].

Treatment prognostic factors, also known as predictors, are variables that predict response to any treatment, whereas treatment prescriptive factors, or moderators, predict a differential response to different treatments [13]. There is a growing interest in the topic of predictors and moderators of outcomes, although there is still limited knowledge of outcome predictors and moderators in the mental health field [14]. The identification of reliable moderators has been particularly difficult. At least two meta-analyses and two reviews [2,11,15,16] have provided evidence of the potential for baseline variables to moderate outcomes, including demographics (e.g., age, employment status), features of depression (e.g., overall symptom severity, specific symptoms), comorbid mental disorders (e.g., anxiety) or personality style, as well as other features (e.g., childhood trauma).

Research on moderators of depression treatment efficacy has focused mainly on CBT, IPT, antidepressant medication, or combinations of the latter with some of these types of psychotherapy [11]. Although the PPI approach can help to broaden the treatment options for depression (e.g. [17,18]), little is known about moderators of these positive interventions [19,20]. To our knowledge, none of the studies that have directly compared CBT and PPI in depression (e.g. [21–26]) have analyzed moderators that are associated to better therapeutic outcomes for each modality. The goal of personalizing interventions, based on research of moderators has been clearly articulated in the positive-activity fit model [27] which proposes that features of positive activities (e.g., timing, variety), persons and, ultimately, person-activity fit may moderate the effect of positive interventions on well-being. In this line, there have been recent attempts to find moderators of different modalities of PPI, such as personality characteristics, personal preferences and baseline level of the feature for which the intervention is designed [20,28,29].

### 1.2. Combined indexes of moderation

One issue with the existing literature on moderators is that it has mainly focused on the effect of individual moderators [13]. However, moderators tend to have small effects and evidence suggest that response to treatments for depression is likely the product of multiple moderators [2,30]. Accordingly, combined moderator indexes have recently been developed [30,31]. One such example, the Personalized Advantage Index (PAI) proposed by DeRubeis et al. [31], is based on algorithms that identify the treatment predicted to produce the better outcome for a given patient. They provide, for each patient, a quantitative estimate of the magnitude by which one treatment is predicted to outperform the other [13,31]. In randomized clinical trials, one way of testing the utility of the approach is by comparing the outcomes of those who had been randomly assigned to their indicated treatment versus those assigned to the “non-indicated” treatment. In previous studies, the PAI approach has shown promise as a mean of predicting differential outcomes to interventions, particularly for patients who are predicted to have larger differences in response to treatments (e.g. [31,32]) or larger probability of dropout [33].

### 1.3. The present study

The aim of this study was to identify moderators of the differential efficacy of two psychological group interventions for clinical depression and to create a combined index of predictors and moderators to predict the optimal treatment for each individual patient. For this purpose, the treatment selection method developed by DeRubeis et al. [31] was applied as a post-hoc analysis of data from a recently published trial comparing the efficacy of a CBT group intervention and a positive psychology group intervention (IPPI-D) for clinical depression [7,8,34]. Results showed that both intervention programs were statistically and clinically effective as well as highly acceptable for clinically depressed participants, with no significant differences either in the main (i.e., severity of depressive symptoms, clinical diagnosis) or secondary (e.g., emotional functioning, well-being) outcomes.

Despite lack of differences between treatments, there may be important differential effects for some groups of patients that could guide treatment assignment for patients. The PAI was calculated in this exploratory study to identify the intervention predicted to produce the better outcome for a given patient. The present study included a large number of potential moderators in the analyses. In addition to the traditional pool of variables, this study includes positive functioning variables that are often neglected but may be very relevant for clinical depression [35].

## 2. Methods

### 2.1. Participants and procedures

A comprehensive description of the participants and procedures can be found in previous publications [7,8,36]. Participants were recruited in a women's center, linked to the community health centers system, which periodically offers group interventions for depression. Participants were 128 women between the ages of 27 and 83 (mean age: 52.02; SD: 10.58) who met criteria for a DSM-IV diagnosis of major depression or dysthymia, using the SCID structured interview (Structured Clinical Interview for the DSM-IV [37]). Due to restrictions where the treatments were offered, participants could not be randomly assigned to the Integrative Positive Psychological Intervention for Depression (IPPI-D; n = 62) and the CBT (n = 66). Yet, participants were blind to the type of treatment they would receive as the two treatments were offered as programs for depression without any further details on their contents (see [7] for further details on assignment). The women signed an informed consent to participate in the study and answered some demographic and clinical questions through a structured interview (e.g., previous psychological or pharmacological treatments, family history of mental problems). The University Ethics Committee approved the study protocol. Exclusion criteria included: present substance abuse or dependence disorder, past or present manic or hypomanic episodes, past or present psychotic disorder, and a cognitive disorder (e.g., dementia or intellectual disability) that might prevent participants to follow the interventions.

### 2.2. Intervention conditions

CBT and IPPI-D were each delivered in 10 weekly, 2 hour sessions of group intervention (five groups of each condition were conducted with 10–15 participants each). CBT was adapted from the widely used Coping with Depression course [38,39]. IPPI-D was designed using positive empirically-validated interventions ([17,18] - for further details, see Chaves et al. [7,36]).

### 2.3. Measures

The Beck Depression Inventory II (BDI-II; [40,41]; α = 0.87) assesses depressive symptomatology. In this analysis, baseline (0 months) and post-treatment (3 months) scores on the BDI-II were used. On average, participants were severely depressed (CBT: M = 37.42, SD = 10.68; IPPI-D: M = 34.66, SD = 10.13) and presented high comorbidity [8]. Treatment condition was a binary variable and referred to either CBT or IPPI-D. Hypothesized predictors were measured at baseline and are displayed in Table 1.

### 2.4. Analytic plan

#### 2.4.1. Variables

Change in depressive symptoms was the dependent variable, operationalized as the residualized change in the BDI-II. It was calculated by regressing raw change scores on baseline BDI-II symptoms. For each individual patient, the model-based residual (i.e., the amount of symptom change that is not accounted for by baseline depression) is added to the average group change. End-of-treatment scores were available for 102 participants (79.7% of total sample).

The candidate moderators were chosen from the available variables assessed in the study [7]. The variable selection was conducted taking into account both theoretical and empirical considerations (see Table S1 in the Supplementary materials for information supporting variables selected). A total of 21 variables were chosen following the criteria that are displayed in the Supplementary materials. Missing data (< 10%) were imputed using non-parametric missing value imputation method based on random forests (R package 'missForest' [42]). The variables were then prepared to be entered in the prediction model (see Supplementary materials). Prediction models were developed by including individuals who had missing data, which is consistent with best practices in handling missing data, maintain a larger sample size than listwise deletion, and does not bias the association between outcomes and baseline co-variates [43].

#### 2.4.2. Variable selection

Variable selection was a two-step process [13]. First, to reduce the number of variables under consideration, we submitted them to a bootstrap-aggregated model-based recursive partitioning via random forests using the R package 'mobForest' [44]. In model-based recursive partitioning by random forests, model-based trees are constructed based on bootstraps of the original sample. The first parameter in the model is the regression of residualized change on the treatment condition. The analysis searches for splits in the sample that alter the first parameter (i.e., that suggest differential efficacy of the treatments in a subgroup of patients). Second, the variables that were indicated by this procedure to be robust moderators of treatment differences were then entered in penalized regression equations, by treatment, using elastic net regularization (ENR), with 10-fold cross-validation. ENR penalizes the fit of linear regressions. This shrinks the size of regression coefficients which makes them less susceptible to overfitting. The penalization procedure also doubles as a means of excluding variables from the set that will be used in calculating patients' PAI scores. A variable is excluded when its coefficient is shrunk to zero. For further details, see the Supplementary materials.

#### 2.4.3. Building a Personalized Advantage Index (PAI)

To build a PAI from this regression model, we followed the methods outlined by DeRubeis et al. [31] once moderators had been identified. The PAI represents the expected difference between a patient's optimal treatment and his/her non-optimal treatment. For example, if a model, when applied to a set of values on the baseline variables given by a patient, predicts that the patient would improve 15 BDI points on PPI but 20 BDI points on CBT, the PAI for that patient is a +5.0, indicating a prediction that CBT was the optimal treatment. To quantify the potential effect of matching all patients to their indicated treatment, we compared the outcomes of patients assigned to their optimal treatment versus those assigned to their non-optimal treatment. A detailed description of the building of the PAI can be found in the Supplementary materials.

**Table 1**
Candidate variables per domain.

| |
|---|
| Domain 1: Depression |
| Type of depression (chronic or dysthymia; recurrent) (SCID-I) |
| Previous pharmacological treatment (0 = no, 1 = yes) |
| Previous psychological treatment (0 = no, 1 = yes) |
| Domain 2: Demographics |
| Age |
| Marital status (1 = no partner, 0 = partner) |
| Employment status (1 = no active employment, 0 = active employment) |
| Domain 3: General functioning |
| Comorbid Axis I Diagnosis (SCID-I; 0 = no, 1 = yes) |
| Comorbid Axis III Diagnosis (SCID-I; 0 = no, 1 = yes) |
| Current ADM treatment (0 = no, 1 = yes) |
| Axis IV Diagnosis of Psychosocial and Environmental problems (SCID-I; 0 = no, 1 = yes) |
| Domain 4: Clinical symptoms |
| Difference between cognitive and non-cognitive depressive symptoms (BDI-II) |
| Automatic thoughts (ATQ-30) |
| Negative affect (PANAS) |
| Anxiety (BAI) |
| Domain 5: Positive functioning |
| Positive affect (PANAS) |
| Optimism (LOT-R) |
| Satisfaction with Life (SWLS) |
| Personal growth (PWBS) |
| Positive relations (PWBS) |
| Behavioral activation system (BAS) |

*Note.* ADM = Antidepressant medication; ATQ-30 = The Automatic Thoughts Questionnaire; BAI = Beck Anxiety Inventory; BAS = Behavioral Activation Scale; BDI-II = Beck Depression Inventory; LOT-R = Life Orientation Test Revised; PANAS-NA = Positive and Negative Affect Schedule, Negative Affect subscale; PANAS-PA = Positive and Negative Affect Schedule, Positive Affect subscale; PWBS = Psychological Well-Being Scales; SCID = Structured Clinical Interview for the DSM-IV; SWLS = Satisfaction with Life Scale.

## 3. Results

Descriptive statistics are presented in Table 2. The treatment condition was not a significant predictor of residualized change on the BDI. Yet, there was a nonsignificant tendency suggesting more improvement in IPPI-D than in CBT (B = 2.99, SE = 1.68, $t = 1.78$, $p = 0.08$, $d = 0.31$).

The model-based recursive partitioning suggested that 6 of the 21 variables were moderators. In order of importance, the variables were: a) having an Axis III medical condition; b) a history of prior treatment with antidepressants; c) having an Axis I additional diagnosis; d) baseline ATQ scores, e) baseline personal growth-PWBS scores, and f) the difference between the cognitive and non-cognitive subscales of the BDI[1] (BDI difference). The other variables did not moderate treatment

[1] *BDI Difference*: Supported by previous factor analyses on the structure of symptoms of depression [45], this variable resulted of subtracting the scores on the non-cognitive items from the scores on the cognitive items of the BDI-II. To create the variable we followed the classification of Steer, Ball, Ranieri, & Beck

**Table 2**
Descriptive statistics for baseline variables.

| Variable | IPPI-D (n = 62) | | CBT (n = 66) | |
|---|---|---|---|---|
| | Mean or % | SD | Mean or % | SD |
| Previous pharmacological treatment | 54.8% | – | 65.2% | – |
| Comorbid Axis I Diagnosis (SCID-I) | 48.4% | – | 65.1% | – |
| Panic and/or Agoraphobia[a] | 35.5% | | 33.3% | |
| PTSD[a] | 6.5% | | 5.5% | |
| Social Phobia[a] | 0 | | 3.7% | |
| Generalized Anxiety[a] | 54.8% | | 55.5% | |
| Eating disorder[a] | 3.2% | | 0 | |
| Unspecified anxiety[a] | 0 | | 1.8% | |
| Comorbid Axis III Diagnosis (SCID-I) | 37.5% | – | 37.9% | – |
| Difference between cognitive and non-cognitive depressive symptoms (BDI-II) | −10.73 | 4.95 | −11.52 | 4.98 |
| Automatic thoughts (ATQ-30) | 84.88 | 27.46 | 87.96 | 27.86 |
| Personal growth (PWBS) | 13.56 | 4.83 | 13.01 | 4.82 |

*Note.* None of the differences between groups in these variables were statistically significant. [a] = Percentage from the total number (N = 54) of Axis I comorbidities; ATQ-30 = Automatic Thoughts Questionnaire; BDI-II = Beck Depression Inventory; CBT = Cognitive-Behavioral Therapy; IPPI-D = Integrative Positive Psychological Intervention for Depression; PWBS = Psychological Well-Being Scales; SCID = Structured Clinical Interview for the DSM-IV.

outcome above and beyond what would be expected by chance. We stratified the sample by treatment to explore the effect of these variables on outcomes, as given by the elastic net. Four of them, Axis I comorbidity, Axis III medical conditions, prior antidepressants treatment, and high baseline personal growth-PWBS scores predicted less change in both treatment conditions. However, these variables were stronger predictors of change in the CBT than in the IPPI-D condition (see Table 3). Additionally, baseline ATQ and BDI difference scores predicted less improvement in the CBT, while, in the IPPI-D condition, higher scores actually predicted more overall improvement. Fig. 1 shows the moderation pattern of ATQ, which parallels the pattern of BDI difference moderator.

### 3.1. Predicted outcomes and PAIs

Overall, the model-based predicted scores significantly predicted residualized change on the BDI ($R^{2pred} = 0.12$, $p < 0.001$). The "true" error of prediction (i.e., the average deviation from each patient's actual score) was 7.20 (SD = 5.32). Using the identified moderators, PAI scores were calculated for each individual patient, by subtracting the predicted outcomes in each of the two therapies for that patient, when they were apart in a 10-fold "held-out" sample. The average PAI score was 4.02 (SD = 2.69). The positive value was expected, as it reflects the (non-significant) advantage of IPPI-D observed in this sample.

The model identified that the assignment of participants allocated sixty-five patients to their predicted optimal treatment (see Fig. 2). These patients experienced superior outcomes ($M = 15.59$, SD = 10.03) to patients who, by chance, were assigned to the treatment that was predicted to be suboptimal ($M = 13.29$, SD = 9.04). However, this average difference was small ($d = 0.24$) and not statistically significant [$t(126) = -1.37$, $p = 0.18$].

IPPI-D was predicted to be the optimal treatment for a majority (73%) of the participants. Among these ninety-three patients, IPPI-D ($M = 14.94$, SD = 9.43) produced greater change than did CBT ($M = 11.33$, SD = 9.65, t(91) = −1.82, $p = 0.07$, $d = 0.37$), although the effect was marginally significant. Among the thirty-five patients (27% of the sample) for whom the model predicted that CBT would be the optimal treatment, outcomes did not differ between CBT (M = 17.18, SD = 8.08, and IPPI-D (M = 19.05, SD = 9.05, t (33) = 0.65, $p = 0.52$, $d = 0.21$).

Because many patients had PAI scores close to 0, which indicated that there is little to none difference in predicted outcomes between the treatments, we repeated the analyses above focusing on patients with PAI scores ≥3 (i.e., clinically significant advantage). The results showed an overall benefit of being randomly assigned to one's "optimal" treatment (M = 16.54, SD = 9.32) vs. not (M = 10.41, SD = 9.40, t(71) = −2.77, $p = 0.007$, $d = 0.65$). Examining the outcomes by treatment condition again suggested that for the subsample for which CBT was the hypothetical optimal treatment there was no effect of treatment selection ($t(11) = -0.09$, $p = 0.93$, $d = -0.05$). For the subsample for which IPPI-D was the hypothetical optimal treatment, patients had much better outcome if they were assigned to IPPI-D ($M = 16.43$, SD = 10.28) than if they were assigned to CBT ($M = 9.38$, SD = 9.06, $t(58) = -2.80$, $p = 0.007$, $d = 0.72$).

## 4. Discussion

This study aimed to identify moderators of the differential efficacy of CBT and IPPI-D for clinical depression and to predict the optimal treatment for each patient by combining information from the moderators. Within the approaches for personalization of interventions, the one used in this study (i.e., using data from comparative trials to estimate individualized metrics that predict the optimal treatment for each patient), has been a recommended method [11,47].

As Barlow et al. [12] have pointed out, one of the main limitations of current psychological treatments is that they are designed to treat a specific disorder, whereas most patients present comorbid psychological or medical conditions. Personalizing treatments based on comorbidities and baseline characteristics such as those highlighted in this study may help to improve their efficacy. In the current study, comorbid psychiatric symptoms and prior use of antidepressants were found to be significant moderators. These results are in line with previous studies [11,15]. For example, having received antidepressants has been found to be a moderator in previous comparisons of CBT vs. antidepressants [31,32].

We also found that a variable reflecting positive functioning at baseline (i.e., score on a scale of personal growth) was related to subsequent change. Patients who reported having experienced more growth in the recent past showed more improvement in the PPI condition, relative to CBT. This may suggest that PPIs are better able to activate growth experiences in individuals irrespective of baseline of personal growth. Previous research has linked higher levels of positive emotions to psychological growth after adversities (e.g. [48]). Since IPPI-D includes several modules devoted to increase positive emotions, it is possible that these efforts decrease depression, irrespective of positive growth. Variables like optimism and positive emotionality have been found to play a mechanistic role in CBTs for depression (e.g. [49]) although CBT is not meant to directly increase 'positive' outcomes. Thus, there may be a "ceiling effect" with growth in CBT, such that patients who already have elevated levels of growth do not experience full benefits from treatment.

Negative cognition was also found to be a significant moderator. Specifically, patients characterized by a pattern of increased automatic negative thoughts, as well as those who presented a profile of predominant cognitive depressive symptoms, showed greater change in the

(*footnote continued*)
[46] of the BDI-II Cognitive subscale (i.e., pessimism, past failure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, and worthlessness) and the BDI-II Non-cognitive subscale (i.e., sadness, loss of pleasure, loss of interest, indecisiveness, loss of energy, irritability, change in appetite, concentration difficulty, tiredness & fatigue, loss of interest in sex, crying, agitation, and changes in sleeping). If the variable Difference between cognitive and non-cognitive depressive symptoms has a negative value means that the non-cognitive symptoms are more prominent in the specific patient.

**Table 3**
Moderators included in the model for the full sample and in 10-fold cross-validation splits.

| CBT | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intercept | 13.54 | 13.63 | 13.21 | 13.72 | 13.33 | 13.57 | 13.66 | 13.60 | 13.67 | 13.61 | 13.33 |
| Axis III medical condition | −2.22 | −2.28 | −2.43 | −2.10 | −2.46 | −2.51 | −2.19 | −1.55 | −1.57 | −2.43 | −2.49 |
| Prior treatment with antidepressants | −2.01 | −2.12 | −1.32 | −2.09 | −1.96 | −1.94 | −2.22 | −2.52 | −1.80 | −2.24 | −2.05 |
| Axis I co-morbid diagnosis | −2.15 | −2.12 | −2.67 | −1.80 | −2.33 | −2.01 | −2.16 | −1.77 | −2.21 | −2.46 | −2.07 |
| Baseline ATQ scores | −1.02 | −1.09 | −0.70 | −1.09 | −1.24 | −0.64 | −0.87 | −1.53 | −0.45 | −1.26 | −1.46 |
| Baseline personal growth-PWBS scores | −1.92 | −1.87 | −1.42 | −1.96 | −2.00 | −1.51 | −2.17 | −1.76 | −1.89 | −1.92 | −2.67 |
| Baseline BDI-II difference scores | −0.56 | −0.54 | −0.48 | −0.42 | −0.59 | −0.80 | −0.32 | 0.21 | −0.94 | −0.84 | −0.84 |

| IPPI-D | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intercept | 16.01 | 16.08 | 15.46 | 15.98 | 15.93 | 16.44 | 16.13 | 15.91 | 16.35 | 16.06 | 15.73 |
| Axis III medical condition | −0.80 | −1.05 | −0.81 | −0.29 | −0.97 | −0.70 | −1.26 | −0.70 | −0.65 | −0.85 | −0.74 |
| Prior treatment with antidepressants | −0.02 | 0.27 | 0.02 | −0.25 | −0.05 | 0.09 | 0.12 | −0.32 | −0.09 | 0.06 | −0.06 |
| Axis I co-morbid diagnosis | −0.40 | −0.30 | −0.70 | −0.36 | −0.36 | −0.50 | −0.25 | −0.34 | −0.21 | −0.33 | −0.61 |
| Baseline ATQ scores | 1.20 | 1.12 | 1.55 | 0.69 | 1.31 | 1.22 | 1.02 | 1.25 | 1.14 | 1.22 | 1.38 |
| Baseline personal growth-PWBS scores | −0.21 | −0.42 | 0.05 | −0.10 | −0.14 | −0.13 | −0.57 | −0.02 | −0.23 | −0.20 | −0.23 |
| Baseline BDI-II difference scores | 0.62 | 0.52 | 0.57 | 0.24 | 0.71 | 0.97 | 0.71 | 0.75 | 0.60 | 0.68 | 0.55 |

*Note.* = Alphate; ATQ = Automatic Thoughts Questionnaire; BDI-II = Beck Depression Inventory; CBT = Cognitive-Behavioral Therapy; IPPI-D = Integrative Positive Psychological Intervention for Depression; PWBS = Psychological Well-Being Scales.

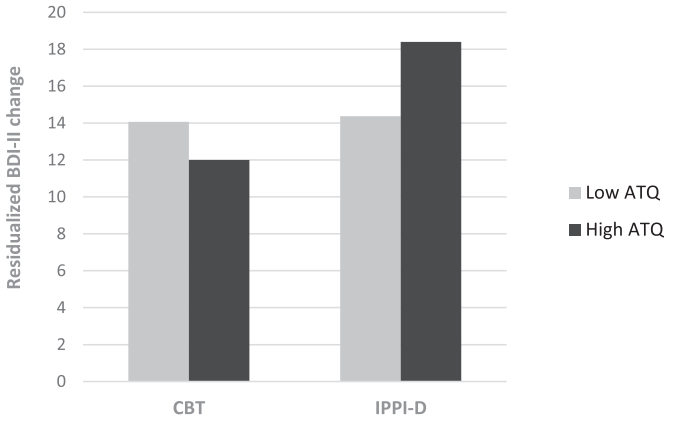


**Fig. 1.** BDI change by ATQ level and intervention condition.
*Note.* ATQ = Automatic Thoughts Questionnaire; BDI-II = Beck Depression Inventory; CBT = Cognitive-Behavioral Therapy; IPPI-D: Integrative Positive Psychological Intervention for Depression. =

positive intervention. It could be possible that standard formats of CBT, as the one used in this study, focused on working with negative cognitions, may be particularly difficult for patients with high levels of this type of cognitions. In these cases, unsuccessful attempts to change negative cognitions may result in frustration and, eventually, rumination or use of thought suppression rather than cognitive restructuring. This explanation is congruent with growing evidence showing that repetitive patterns of negative thinking are related to cognitive biases and cognitive control deficits (e.g. [50,51]). Some of the most central CBT techniques, like cognitive reappraisal, seem to require substantial cognitive effort [52,53], and this may be problematic for those patients with more severe depressive symptoms or who are more prone to ruminate (e.g. [54]). These hypotheses will require further investigation, as research on the relation between cognitive control deficits and emotion regulation difficulties is still in its infancy [55].

In contrast, positive interventions may overcome dysfunctional cognitions through direct changes in quality of life of patients and by increasing the focus on daily positive emotions. At least one prior RCT found that focusing on individual's' strengths, rather than attempting to overcome their weaknesses, was a more effective treatment for depression [56]. Although the apparent advantage of a positive intervention over CBT in clinically depressed patients with frequent dysfunctional cognitions seems to be counterintuitive, the NIMH Collaborative Study on Depression showed that higher intensity of dysfunctional beliefs predicted a superior response to IPT, relative to either CBT or antidepressant medication coupled with clinical management [57]. Similarly, Huibers et al. [32] applied the PAI method in a comparative study of CBT and IPT. In their study, patients with more interpersonal problems and external triggers benefitted more from CBT, whereas IPT was superior for patients with cognitive dysfunction and low interpersonal problems and fewer external triggers. Thus, for

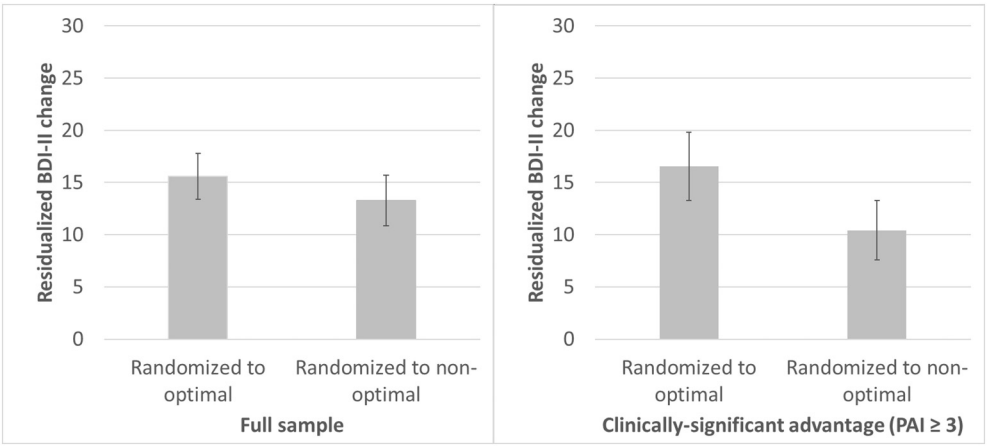


**Fig. 2.** Observed advantage of treatment selection.
*Note.* Comparison of mean residualized BDI-II change for patients randomly assigned to their optimal treatment versus those assigned to their non-optimal treatment. The left graph gives the results for the full sample. The right graph includes only patients for whom the algorithm predicted a clinically significant advantage on the Personalized Advantage Index (PAI) of ≥3. BDI-II = Beck Depression Inventory. Error bars indicate 95% confidence interval (CI).

patients with a high frequency and intensity of negative cognitions, CBT may be a relatively poor choice of treatment, relative to other evidence-based treatments (see for a similar result [58]).

Overall, our results suggest the need for further treatment selection efforts, as data-driven approaches may be better suited than theory-based expectations for the purpose of finding the best fit of persons to treatments. The PAI model yielded some additional interesting results. When predicting for each patient which treatment was more likely to lead to better outcomes, results showed an overall advantage of IPPI-D over CBT, albeit with substantial variability in the sample. The PAI model predicted that most patients (73%) would experience greater improvement if assigned to IPPI-D than to CBT in this sample. Although marginally significant, the effect size of 0.37 of this difference appears larger than most reported differences between types of psychotherapies [59], which may be taken to suggest that it is a clinically important effect. Besides this overall advantage of being assigned to IPPI-D, there was an interesting difference between both therapeutic conditions. For patients whose optimal treatment was identified as CBT (27% of the sample), being assigned to the IPPI-D condition did not predict poor outcomes. On the contrary, for patients whose optimal treatment was IPPI-D, being assigned to the CBT was associated to less change in depression. One explanation of this finding could be that the variables associated with a *relatively* better response to CBT in our study are the ones that are typically associated with a good prognosis (e.g., being treatment-naïve, no comorbidities) [15], thus suggesting good outcomes irrespective of which treatment was received. This study's sample, middle-aged adults presenting a high degree of comorbidity (see [8]), fit with the patient profile that seems to be more benefited from IPPI-D. This may partially explain the relative superiority of the IPPI-D found in the results. In other samples, this same PAI model may predict that more patients would benefit from CBT.

To our knowledge, this is the first study that analyzes moderators of differential efficacy of PPI vs CBT and, therefore, the results must be interpreted with caution. Only two specific intervention programs were compared, so the results are constrained to such comparison until more studies are conducted with a variety of interventions or treatment modalities. Additionally, the format of interventions delivery, as a group intervention, and the limited number of sessions (10 weekly sessions), might have influenced the findings. Research based on personalization of treatments is in its infancy and it would be necessary to compare different interventions in diverse contexts, formats of delivery and different dosages. The characteristics of the study's sample (i.e., only women, mean age of 52 years old) also limit the conclusions of the study because the variables that resulted as moderators in this specific sample (e.g., Axis III comorbidity and prior treatment with antidepressants) may have not been selected in other samples with different inclusion criteria. Furthermore, gender may be a moderator in itself and this study cannot account for its potential effect. Finally, the relatively small sample size, although similar to the samples generally used in treatment selection studies, is also a limitation of the study. Since this is an exploratory study, other randomized trials, using larger and more heterogeneous samples, would be necessary to verify the validity of the present model [30].

The future of clinical psychology should be one in which interventions are tailored to the patient in dosage, combination of components within and between psychological approaches, format of delivery (e.g., group or individual), specific context, needs and therapist/patient preferences. Overall, this study suggest that new multivariable treatment selection approaches as the PAI can be useful tools to develop this kind of precision mental health care [13].

## Acknowledgments

This research was partially supported by the Spanish Ministry of Economy (MINECO) grants (PSI2015-69253-R, PSI2014-61764-EXPLORA) and by a scholarship from the Ministry of Education, Culture and Sports (FPU12/02342). We would like to thank Loreto de la Carrera and the Concejalia de Igualdad del Ayuntamiento de Fuenlabrada for their continuous support of the study, and to Jack Keefe, Colin Xu, Zachary Cohen, Silvia Moreno, Trinidad Soria, Almudena Duque, Natalia Poyato, Pablo Roca, Ivan Blanco, Teodoro Pascual, Laura Machado, Alina Rigabert, Regina Espinosa, Marta Fernandez-Salineros, Beatriz Fernandez, Vanesa Agudo, Nerea Barrachina, Victoria Guillen, and Ariadna de la Vega for their collaboration at different stages of this research. We also thank Rosa Maria Zangri for helping us to edit the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.07.004.

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